The Tryptophan Partition

A Shared Metabolic Substrate in the Bioenergetic Architecture of Neurodegeneration

Kynurenine, NAD+, Serotonin, and Tryptamine as Branch Points of a Single Substrate Whose Allocation Collapses in Parallel with Mitochondrial, Microglial, and Synaptic Decline

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A Dissertation Submitted in Partial Fulfillment of the Requirements for the Degree of Doctor of Philosophy in Neuroscience. Fourth in the Collapse trilogy, companion volume to Convergent Synaptic Collapse, Homeostatic Microglial Collapse, and Bioenergetic Collapse.

“Tryptophan is the rarest of the amino acids and the most prodigal of them — it is spent in four directions at once, and the brain knows the cost of each.”

— ONS Methodology Working Notes, 2026

For Oskar Fischer, whose century-old observation that the inflamed glial response was not a bystander to neurodegeneration but a participant in it anticipates, by 120 years, the immunometabolic framework on which this dissertation depends.

THE COLLAPSE TRILOGY — COMPANION VOLUME

I. Convergent Synaptic Collapse

II. Homeostatic Microglial Collapse

III. Bioenergetic Collapse

IV. The Tryptophan Partition ☐ this volume

The trilogy's three principal volumes address distinct axes of neurodegenerative collapse — synaptic circuit, microglial state, and bioenergetic substrate. The present companion volume identifies tryptophan as the single metabolic variable whose partition across four catabolic branches couples the three axes through a shared substrate. It is situated in the bioenergetic section because the NAD^+ de novo branch and its integration with the integrated stress response are the load-bearing connections, but the framework extends across the trilogy.

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Abstract

Tryptophan is the rarest of the proteinogenic amino acids and the only one whose catabolism opens onto four mechanistically independent downstream branches relevant to neurodegeneration: the kynurenine pathway, which terminates either in the excitotoxic NMDA agonist quinolinic acid or the neuroprotective antagonist kynurenic acid; the de novo NAD+ biosynthesis branch, which provides one of two cellular routes to the cofactor on which oxidative phosphorylation, sirtuin signaling, PARP-mediated DNA repair, and the integrated stress response all depend; the serotonergic branch, which yields 5-hydroxytryptamine, melatonin, and the trophic signaling that supports adult hippocampal neurogenesis and synaptic plasticity; and the microbiota-derived tryptamine branch, which has been argued to competitively inhibit tryptophanyl-tRNA synthetase and corrupt the first step of protein biosynthesis. Each branch terminates on a different axis of the Collapse trilogy, and each is regulated by enzymes whose expression is modulated by neuroinflammation, hypoxia, oxidative stress, and the integrated stress response. This dissertation advances the thesis that tryptophan is best understood not as a contributor to any one disease mechanism but as a *partition node*—a shared upstream substrate whose allocation across branches is itself a disease-relevant variable, and whose maladaptive reallocation under inflammatory and bioenergetic stress drains supply from neuroprotective branches into neurotoxic ones.

The thesis is organized in seven analytical chapters. Chapter I traces the biochemistry of tryptophan catabolism, locating the partition at the IDO1/IDO2/TDO branch point and characterizing the regulatory inputs that bias allocation. Chapter II examines the kynurenine cascade and its excitotoxic terminus, integrating Balin's pathogen-driven IDO induction model with the broader literature on quinolinic-acid/kynurenic-acid imbalance in neuroinflammation. Chapter III treats de novo NAD+ biosynthesis as a tryptophan branch coupled to the integrated stress response, drawing the ATF4/PARP/LC bioenergetic axis through tryptophan supply. Chapter IV examines the serotonergic branch and its consequences for adult neurogenesis, BDNF signaling, and the SSRI therapeutic rationale. Chapter V

analyzes the microbiota-tryptamine-TrpRS axis articulated by Paley, connecting peripheral aminoacylation failure to central proteinopathy. Chapter VI synthesizes the four branches into a partition framework, deriving the formal claim that inflammatory IDO induction is the single most consequential shunt in adult neurochemistry because it simultaneously withdraws tryptophan from the serotonergic branch, biases the kynurenine branch toward quinolinic-acid production, and drives a delayed and incomplete repletion of NAD+ that the integrated stress response then converts into a maladaptive sustained signal. Chapter VII develops therapeutic implications and falsifiable predictions, including the case for kynurenine 3-monooxygenase inhibition, IDO modulation, and combined NAD+ precursor / tryptophan-loading regimens.

The dissertation concludes that the Collapse trilogy's three axes—bioenergetic, microglial, synaptic—are not merely correlated; they are coupled through a common substrate whose allocation collapses in parallel with each axis. The tryptophan partition is the single metabolic variable that touches all three.

Keywords: tryptophan, kynurenine pathway, indoleamine 2,3-dioxygenase, quinolinic acid, kynurenic acid, NAD+ de novo biosynthesis, serotonin, adult neurogenesis, tryptamine, tryptophanyl-tRNA synthetase, integrated stress response, neurodegeneration

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1. Introduction

1.1 The Research Problem

The neurodegenerative diseases are conventionally addressed one pathway at a time. The amyloid cascade hypothesis fixes attention on Aβ; the synucleinopathy hypothesis on misfolded α-synuclein; the mitochondrial cascade hypothesis on respiratory complex decline; the neuroinflammation hypothesis on microglial state. Each framework supplies a vocabulary in which a specific mechanism can be elaborated, but each is also organized around its preferred molecule, and the interfaces between frameworks remain underdeveloped. The Collapse trilogy of which this dissertation forms the fourth volume — *Convergent Synaptic Collapse*, *Homeostatic Microglial Collapse*, and *Bioenergetic Collapse* — was an attempt to articulate the convergent infrastructure on which these disease-specific mechanisms run. The trilogy identified three axes: a synaptic-circuit axis (PV+ interneurons, perineuronal nets, gamma oscillations), a microglial-state axis (loss of TGF-β/SMAD-maintained homeostatic identity), and a bioenergetic-substrate axis (mitochondrial quality-control failure, NAD+ depletion, autophagy-lysosomal collapse).

A question the trilogy did not fully answer is the question of metabolic coupling. The three axes are coupled — that much is evident from the literature on TREM2-PI3K-AKT-mTOR support of microglial OXPHOS (Ulland et al., 2017), from the literature on v-ATPase ATP-dependence as the connection between mitochondrial output and lysosomal acidification (Mindell, 2012; Lee et al., 2022), and from the literature on PV+ interneuron energetics as the substrate for gamma-frequency firing (Kann et al., 2014). But coupling at the level of *cofactor exchange* and *substrate exchange* — the level at which one axis's metabolic demand draws from a pool that another axis also draws from — has remained largely implicit.

The present dissertation argues that tryptophan is such a shared pool, and that its allocation across the four downstream branches that consume it is a measurable, disease-relevant variable that the trilogy has not yet integrated.

This dissertation addresses the question: **What role does tryptophan partition across its catabolic branches play in the bioenergetic architecture of neurodegeneration?** The thesis advanced is that tryptophan is a partition node whose maladaptive allocation under sustained neuroinflammatory and bioenergetic stress is a unifying upstream variable connecting the Collapse trilogy's three axes — and that the inflammatory induction of indoleamine 2,3-dioxygenase (IDO) is the single most consequential shunt in the system because it withdraws tryptophan from neuroprotective branches and routes it through a kynurenine cascade whose default terminus, under microglial activation, is the excitotoxic NMDA agonist quinolinic acid.

1.2 Significance

The significance of this reframing is fourfold. First, it identifies a *metabolic*, rather than a proteomic or a transcriptional, coupling variable between three independently characterized disease axes. Tryptophan is one of nine essential amino acids in adult humans; it is by far the rarest in the proteome (approximately 1% of residues by frequency), it is the precursor for two neuroactive small-molecule classes (the indoleamines and the kynurenines), and it is the upstream substrate for one of two routes by which mammalian cells synthesize NAD+. A single amino acid that simultaneously regulates excitotoxic signaling, bioenergetic cofactor supply, serotonergic tone, and (through tryptamine) proteostatic fidelity is *a priori* a candidate substrate for systems-level coupling.

Second, the framework supplies a mechanistic interpretation of the long-observed but rarely integrated *peripheral–central* coupling in neurodegeneration. Tryptophan is the only essential amino acid whose plasma concentration is acutely responsive to systemic inflammation through IDO induction in peripheral immune cells, and the plasma kynurenine-to-tryptophan ratio is a validated biomarker of systemic immune activation (Schröcksnadel et al., 2006). The framework therefore makes a clear prediction: peripheral inflammation should produce centrally measurable changes in tryptophan allocation that track with disease trajectory. This prediction is testable and has begun to be validated in PD and

AD cohorts (Lim et al., 2017; van der Velpen et al., 2019).

Third, the framework reorganizes the therapeutic landscape. Where each axis of the trilogy generates its own therapeutic surface — mitophagy inducers, microglial state stabilizers, perineuronal-net protection — the tryptophan partition supplies a *cross-cutting* therapeutic surface: IDO inhibitors (already in clinical use in oncology), kynurenine 3-monooxygenase (KMO) inhibitors (in late preclinical and early clinical development for neuroinflammation), NAD+ precursors (nicotinamide riboside, NMN), and tryptophan supplementation as upstream substrate restoration. The framework also explains why monotherapy on any single one of these targets has been disappointing in the clinic: rebalancing the partition requires interventions at multiple branch points simultaneously.

Fourth, the framework supplies a unifying mechanistic interpretation of a set of otherwise disparate clinical observations: the late-life association of depression with subsequent dementia risk (which the framework attributes to chronic IDO-driven serotonergic withdrawal as an early biomarker of the same inflammatory shunt that later manifests as cognitive collapse); the failure of SSRIs to robustly prevent AD progression (because tryptophan substrate withdrawal upstream of 5-HT synthesis cannot be rescued by reuptake inhibition alone); the apparent neuroprotective signal in some niacin-rich diets (NAD+ precursor restoration partially bypassing the de novo branch); and the long-recognized but mechanistically obscure connection between chronic infections and dementia risk (pathogen-driven IDO induction sustained over years).

1.3 Scope and Limitations

This dissertation is a synthetic review, not a report of original experimental data. Its contribution lies in the integration of literatures from immunometabolism, neuropharmacology, gut–brain axis biology, mitochondrial NAD+ metabolism, and the proteinopathy framework into a single analytical schema centered on tryptophan as a partition node. The work draws principally on Alzheimer's disease because the underlying Collapse trilogy is organized around AD, but the kynurenine and serotonergic literatures extend naturally to PD, ALS, HD, FTD, and major depression, and each chapter addresses the cross-disease evidence where it is informative.

The thesis cannot, and does not attempt to, resolve whether the inflammatory IDO shunt is the *causally upstream* variable in neurodegeneration or whether it is a mid-stream amplifier of insults that originate elsewhere. The framework is consistent with either reading. What it does assert is that tryptophan partition is a sufficiently quantitative, sufficiently coupled, and sufficiently therapeutically tractable variable that it deserves a place in the trilogy alongside mitochondrial quality control, microglial homeostasis, and synaptic circuit integrity. The framework also does not resolve the open question of whether kynurenic acid is, on net, neuroprotective in AD — the evidence is mixed, and Chapter II treats this ambiguity directly.

2. Literature Review

2.1 Historical Foundations: From Hopkins to the Kynurenine Pathway

Tryptophan was identified as a distinct amino acid by Frederick Gowland Hopkins and Sidney Cole in 1901, isolated from casein digests, and shown to be required for normal growth in feeding experiments by Wilcock and Hopkins (1906) — among the earliest demonstrations of essential amino acid biology and a foundational result for nutritional biochemistry. The kynurenine pathway was characterized over the subsequent half-century. Kotake and Masayama (1936) isolated kynurenine from rabbit urine. Heidelberger, Gullberg, Morgan, and Lepkovsky (1949) traced the pathway from tryptophan through formylkynurenine, kynurenine, 3-hydroxykynurenine, 3-hydroxyanthranilic acid, and quinolinic acid, establishing the topology of the catabolic cascade that is still in use. The enzymatic identity of the first and rate-limiting step was the longest-contested issue: tryptophan 2,3-dioxygenase (TDO), expressed primarily in liver, was characterized first (Hayaishi et al., 1957); indoleamine 2,3-dioxygenase (IDO1), expressed broadly and inducible by IFN-γ, was characterized two decades later (Hirata and Hayaishi, 1971; Hayaishi, 1976). The second IDO isoform (IDO2) was identified by Ball et al. (2007).

The discovery that the kynurenine pathway terminates in two endogenous neuroactive metabolites — quinolinic acid (Stone and Perkins, 1981), which is a competitive NMDA receptor agonist with excitotoxic activity at low-millimolar local concentrations, and kynurenic acid (Perkins and Stone, 1982), which is a broad-spectrum ionotropic glutamate receptor antagonist with neuroprotective

activity — transformed the kynurenine pathway from a peripheral catabolic curiosity into a central nervous system signaling system. Schwarcz, Bruno, Muchowski, and Wu (2012) provided the canonical review that consolidated this neurochemistry into a unified framework, and the kynurenine pathway is now treated as a third class of neurotransmitter precursor — alongside the catecholamines and the indoleamines — that derives directly from amino-acid catabolism.

The connection between tryptophan and NAD+ biosynthesis was established by Krehl, Teply, Sarma, and Elvehjem (1945), whose demonstration that tryptophan supplementation could substitute for niacin in pellagra-preventing diets resolved a 50-year nutritional puzzle. The pellagra story is the historical anchor for the present thesis: pellagra is a disease of NAD+ depletion that produces dermatitis, diarrhea, and dementia — the "three Ds" — and its prevention by tryptophan rather than niacin demonstrated that the kynurenine-pathway terminus connects to NAD+ supply. Pellagra-related dementia is, in this reading, the first historically characterized example of tryptophan-partition failure producing neurodegeneration; it is reversible because the underlying lesion is substrate deficiency rather than mitochondrial damage.

2.2 IDO, IFN-γ, and Immunometabolic Coupling

The induction of IDO1 by IFN-γ in monocytes, macrophages, dendritic cells, and microglia (Yoshida and Hayaishi, 1978; Pfefferkorn, 1984) established IDO as the central effector linking innate immune activation to tryptophan catabolism. Munn, Zhou, Attwood, Bondarev, Conway, Marshall, Brown, and Mellor (1998) demonstrated that IDO is required for maternal-fetal immune tolerance — placental trophoblast IDO expression depletes tryptophan from the local maternal lymphocyte microenvironment, suppressing T-cell proliferation. The discovery established IDO as a generalized immunosuppressive mechanism with consequences across all tissues in which it is expressed. The subsequent literature has characterized IDO as a master switch coupling adaptive and innate immunity to amino-acid catabolism: IDO induction depletes tryptophan locally and generates kynurenine metabolites systemically, simultaneously withdrawing substrate from competing branches and producing biologically active downstream effectors.

In the brain, IDO1 is expressed at low levels under homeostatic conditions, primarily in microglia and a subset of endothelial cells. IFN-γ from infiltrating T

cells, IL-1β from activated microglia, and Aβ oligomers all induce IDO1 expression in microglia (Bonda et al., 2010), and CSF and brain-tissue measurements have documented elevated kynurenine-to-tryptophan ratios in AD, PD, and HD cohorts (Guillemin et al., 2005; Lim et al., 2017; Stoy et al., 2005). The TDO isoform is constitutively expressed in liver and is responsible for basal kynurenine production; in disease, however, the bulk of CNS kynurenine derives from local IDO induction in microglia rather than from peripheral TDO output. This distinction matters: TDO-driven kynurenine is constitutive and homeostatic; IDO-driven kynurenine is inflammatory and pulsatile, and the kinetics of IDO induction (hours to days after the inflammatory stimulus, sustained for weeks under chronic stimulation) match the kinetics of microglial activation in neurodegeneration.

2.3 The Quinolinic Acid / Kynurenic Acid Balance

Within the brain, the partition of kynurenine between its quinolinic acid (QUIN) and kynurenic acid (KYNA) endpoints is itself regulated. Kynurenine 3-monooxygenase (KMO) — the enzyme that converts kynurenine to 3-hydroxykynurenine and commits the pathway toward QUIN — is expressed in microglia and infiltrating macrophages but not in astrocytes. Kynurenine aminotransferase (KAT, principally KAT II in adult brain) — the enzyme that converts kynurenine to KYNA — is expressed in astrocytes but not in microglia. The cellular segregation produces a *spatial* partition: microglial activation biases the kynurenine branch toward QUIN, while astrocytic processing biases the same branch toward KYNA (Schwarcz et al., 2012; Guillemin, 2012). This means that the same substrate, kynurenine, can produce opposing neurochemical effects depending on which cell type catabolizes it. In neurodegeneration, the loss of homeostatic astrocyte function combined with sustained microglial activation produces a double shift toward the QUIN-favored terminus: microglial KMO is upregulated, astrocytic KAT is downregulated, and the QUIN/KYNA ratio rises in CSF.

QUIN is a competitive NMDA receptor agonist at the NR2B-containing subset of receptors, the same subset that mediates excitotoxic calcium influx. The QUIN concentrations required for receptor agonism are achievable in inflamed microglial microenvironments. Beyond receptor agonism, QUIN also enhances oxidative stress through complex-I inhibition and pro-oxidant iron complexes, and it is itself a neurotoxin in chronic exposure paradigms (Lugo-Huitrón et al., 2013). KYNA, in contrast, antagonizes NMDA receptors at the glycine co-agonist site, α7-nicotinic

acetylcholine receptors, and aryl hydrocarbon receptor signaling — supplying broad-spectrum dampening of glutamatergic and cholinergic excitation. The QUIN/KYNA balance is therefore the local realization of the kynurenine branch and is itself a partition node nested within the larger tryptophan partition.

2.4 De Novo NAD+ Biosynthesis: The Bioenergetic Terminus

The quinolinic acid produced by the kynurenine pathway is not solely a neurotoxin: it is also the substrate for quinolinate phosphoribosyltransferase (QPRT), which adds a phosphoribosyl group to generate nicotinic acid mononucleotide (NaMN), which is in turn adenylylated to nicotinic acid adenine dinucleotide (NaAD) and amidated to NAD+. This is the *de novo* arm of NAD+ biosynthesis, parallel to the *salvage* arm (which recycles nicotinamide back to NAD+ through NAMPT) and the *Preiss-Handler* arm (which incorporates dietary niacin) (Verdin, 2015; Bogan and Brenner, 2008). In peripheral tissues, the de novo arm contributes only a minor fraction of total NAD+ flux; in the CNS, the relative contribution is regionally variable and has been incompletely characterized. What is clear is that QPRT expression is upregulated under inflammatory and stress conditions and that the de novo arm becomes quantitatively significant precisely when the salvage arm is being overwhelmed — for example, under PARP-1 hyperactivation from DNA damage, where NAD+ is being consumed faster than NAMPT can resupply it.

The integrated stress response (ISR), driven by the master transcription factor ATF4, supplies the regulatory logic that connects the inflammatory and bioenergetic faces of the kynurenine pathway. ATF4 upregulates NAMPT, NMRK1, and tryptophan-pathway enzymes (Mungrue et al., 2009; Han et al., 2013) — the cell's response to NAD+ depletion is simultaneously to refill the salvage pool *and* to enhance de novo synthesis. Because IDO induction is itself an inflammatory response, and IDO induction increases kynurenine flux, the ISR and IDO induction are kinetically coupled: an inflammatory stimulus that activates microglia simultaneously induces IDO and triggers ATF4 in surrounding cells, jointly biasing the partition toward the kynurenine branch *and* toward de novo NAD+ synthesis at the kynurenine terminus. This coupling is the molecular basis of the present thesis's central claim that the tryptophan partition is not a passive distribution but an actively regulated allocation under inflammatory control.

2.5 The Serotonergic Branch and the Hidden Tax on 5-HT Synthesis

Approximately 1–2% of dietary tryptophan in humans is allocated to serotonin synthesis under homeostatic conditions; the remainder is divided between protein synthesis, the kynurenine pathway, and minor branches (Le Floc'h et al., 2011). The 1–2% allocation to 5-HT is small in absolute terms but is the only source of central serotonin, which cannot cross the blood-brain barrier and must therefore be synthesized in the brain from imported tryptophan. The 5-HT synthesis pathway runs through tryptophan hydroxylase 2 (TPH2) — a low-Km enzyme that is normally substrate-saturated — and aromatic amino acid decarboxylase (AADC). Under homeostatic conditions, central 5-HT synthesis is *not* substrate-limited.

Under IDO induction, however, peripheral and central tryptophan concentrations drop, and once tryptophan availability falls below the TPH2 Km, 5-HT synthesis becomes substrate-limited. This is the mechanistic basis for the "inflammation hypothesis of depression" (Maes, 1995; Dantzer et al., 2008): chronic peripheral inflammation reduces central 5-HT synthesis by withdrawing substrate. The same mechanism is implicated in late-life depression as a prodrome of dementia: chronic inflammatory IDO induction depresses 5-HT synthesis, producing depressive symptoms that precede measurable cognitive decline by years to decades, and continued IDO induction over the same period drives the QUIN/KYNA shift and the NAD+ demand that the cognitive collapse later reflects (Leonard, 2017).

The serotonergic branch is also coupled to adult hippocampal neurogenesis. Selective serotonin reuptake inhibitors (SSRIs) increase BDNF expression, promote adult hippocampal neurogenesis, and produce cognitive benefits in some AD models (Mowla et al., 2007; Cirrito et al., 2011). The neurogenesis-restoration argument requires that 5-HT signaling be available at the receptor; if tryptophan partition has already drained the serotonergic branch upstream of synthesis, SSRIs cannot rescue 5-HT levels because the substrate has been withdrawn. The framework therefore predicts an interaction effect: SSRIs should be effective at preventing or delaying AD only in patients whose tryptophan partition has not yet been substantially shunted toward the kynurenine branch, which can be operationalized as a low plasma kynurenine-to-tryptophan ratio.

2.6 The Tryptamine Branch and Proteostatic Fidelity

A separate branch of tryptophan catabolism, principally microbial in origin, produces tryptamine — a biogenic amine that is structurally similar to tryptophan itself and that can competitively interact with tryptophan-handling enzymes. Paley (2019, 2024) has argued that gut-microbiome-derived tryptamine, absorbed through the intestinal epithelium and reaching the brain through the portal-systemic circulation, competitively inhibits tryptophanyl-tRNA synthetase (TrpRS), the enzyme that loads tryptophan onto its cognate tRNA at the first step of protein biosynthesis. On this account, tryptamine-induced TrpRS inhibition produces incomplete or misfolded translation products at tryptophan-rich positions, generating the proteomic substrate from which Aβ, tau, α-synuclein, and other aggregation-prone proteins arise. The framework remains controversial — direct evidence for TrpRS inhibition by physiological tryptamine concentrations in vivo is limited — but it supplies a mechanistically coherent gut–brain axis for proteinopathy that the present thesis acknowledges as a candidate fifth branch of the tryptophan partition.

The tryptamine branch is relevant to the partition framework even if Paley's specific TrpRS mechanism is not the dominant pathway. Microbiota-derived tryptophan metabolites — indole, indole-3-acetate, indole-3-propionate, tryptamine, and others — are aryl hydrocarbon receptor (AHR) ligands, modulating systemic and central immune tone (Hubbard et al., 2015; Rothhammer and Quintana, 2019). Microbial tryptophan utilization withdraws substrate from host kynurenine and serotonergic branches, and microbial AHR-ligand output modulates IDO expression and microglial state. The gut microbiota therefore constitutes a *peripheral partition operator*: its tryptophan consumption and its tryptophan-derived signaling jointly determine how much substrate reaches the host's central tryptophan partition, and how that partition is regulated once the substrate arrives.

2.7 Mitochondrial Coupling and the Locus Coeruleus

The Bioenergetic Collapse thesis (Gustafsson, 2026) identifies the locus coeruleus (LC) as the earliest known site of AD pathology and develops a model in which LC neurons fail through PARP-1 hyperactivation, ISR exhaustion, and NAD+ depletion driven by their unique catecholaminergic biochemistry. The LC argument intersects the tryptophan partition at two points. First, the LC is a *noradrenergic* nucleus, but its survival depends on NAD+ supply, and de novo NAD+ from the kynurenine arm is one of the routes by which ATF4 can resupply the cofactor under stress. The PARP*Locus*Coeruleus*Phase*I working paper explicitly identifies "tryptophan-pathway enzymes" among the ATF4 targets in this resupply program (Gustafsson, 2026, §3.5). Second, the LC's projections include the dorsal raphe nucleus, which is the principal serotonergic nucleus, and LC degeneration alters DRN activity and 5-HT output — propagating tryptophan-partition consequences across the brainstem monoaminergic system. The LC sits, in this reading, at the intersection of the bioenergetic and serotonergic faces of the tryptophan partition; its failure is amplified by both.

2.8 Gaps in the Literature

Five significant gaps in the existing literature motivate the present synthesis. First, the kynurenine, serotonergic, and NAD+ literatures have largely developed in isolation; reviews focused on any one branch treat the others as background context rather than as competing destinations for the same substrate. Second, the partition framing — the explicit treatment of tryptophan allocation as a regulated, disease-relevant variable — is implicit in the immunometabolism literature (Cervenka et al., 2017) but has not been systematically applied to neurodegeneration. Third, the coupling between peripheral IDO induction and central neurotransmitter synthesis is well established in the depression literature but has not been integrated into the broader bioenergetic-collapse framework of dementia. Fourth, the tryptamine/microbiota branch has been treated as a separate gut–brain axis topic rather than as a competitor for the central tryptophan pool. Fifth, the therapeutic implications of partition rebalancing — IDO inhibitors, KMO inhibitors, NAD+ precursors, and substrate restoration — have not been evaluated against a unified partition framework that would predict their interaction effects. This dissertation addresses all five gaps.

3. Methodology

3.1 Disciplinary Approach

This dissertation adopts a systems-level integrative review methodology, synthesizing primary experimental literature, clinical trial data, and theoretical frameworks across immunometabolism, neuropharmacology, gut–brain axis biology, mitochondrial NAD+ metabolism, and neurodegeneration. The approach is consistent with the integrative dissertation tradition established for the Collapse trilogy, in which the contribution lies in the construction of a unifying mechanistic framework rather than in the report of original experimental data.

3.2 Source Selection Criteria

Primary sources were selected for publication in peer-reviewed journals indexed in PubMed/MEDLINE or Web of Science, for experimental methodology adequate to support cited claims, for relevance to one or more of the four catabolic branches that organize the dissertation, and for recency — with preference for publications after 2010 except for foundational work. Review articles are cited for historiographical positioning but are not used as primary evidence for mechanistic claims.

3.3 Analytical Framework

The analysis proceeds through four levels of integration. At the **molecular level**, the biochemistry of each catabolic branch is traced from substrate through committed-step enzyme to terminal product, with attention to regulatory inputs (transcriptional, post-translational, allosteric, and substrate-competition). At the **cellular level**, the partition is examined in its cell-type-specific realization: microglial IDO and KMO expression versus astrocytic KAT expression; neuronal TPH2 substrate dependence; LC neuronal NAD+ demand. At the **systems level**, the partition is examined as a coupled control system, with peripheral inflammation as the principal exogenous regulator and the integrated stress response as the principal endogenous regulator. At the **clinical level**, the framework is evaluated against the disease cohorts in which kynurenine, serotonergic, and NAD+ measurements have been made — principally late-life depression, AD, PD, and HD.

3.4 Citation Protocol

Citations follow APA 7th edition. Primary experimental claims are cited to originating papers rather than to reviews. Where conflicting evidence exists, both sides are cited and the conflict is characterized.

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4. Chapter I — Tryptophan Biochemistry and the Anatomy of a Partition Node

4.1 The Substrate

L-Tryptophan is the rarest of the proteinogenic amino acids by abundance in mammalian proteins (approximately 1.1% of residues by frequency), by dietary supply (a typical Western diet provides 0.5–1.5 g/day, near the lower bound of essential amino acid requirements), and by plasma concentration (50–80 μM in humans, lower than any other essential amino acid). Tryptophan is also the only essential amino acid bound substantially to plasma albumin (75–90% bound), meaning that the *free* tryptophan concentration available for cellular uptake is on the order of 5–15 μM. The blood-brain barrier transports free tryptophan through the large neutral amino acid transporter LAT1 (SLC7A5), which is shared with phenylalanine, leucine, isoleucine, valine, tyrosine, and methionine. Competition at LAT1 is itself a partition mechanism: high circulating concentrations of branched-chain amino acids reduce central tryptophan uptake even without changing plasma tryptophan, while a carbohydrate-induced insulin pulse reduces plasma BCAAs and indirectly increases brain tryptophan uptake — the biochemical basis for the long-recognized association between carbohydrate intake and central serotonin (Fernstrom and Wurtman, 1971).

The cellular consequence of this LAT1 competition is that the central tryptophan pool is small (low micromolar), tightly regulated, and shared across all cells in the brain. There is no dedicated "kynurenine pool" or "serotonin pool" in any cell; there is a single tryptophan pool, and the branches compete for it through the relative activities of their initiating enzymes.

4.2 The Four Catabolic Branches

The partition is structured by the relative activities of four committed-step enzymes that initiate independent downstream cascades:

• **Branch 1 — Protein synthesis.** Tryptophan is loaded onto tRNA^Trp by tryptophanyl-tRNA synthetase (TrpRS, gene *WARS1*) and incorporated into nascent polypeptides at UGG codons. Under homeostatic conditions, this branch consumes the majority of cellular tryptophan flux because protein turnover is the largest amino-acid sink in any cell. TrpRS is substrate-saturated under physiological tryptophan concentrations, which means that small drops in tryptophan availability do not immediately impair translation — but sustained substrate depletion does, and tryptophan codon stalling is a documented consequence of IDO induction in immune cells (Munn et al., 2005).

• **Branch 2 — The kynurenine pathway.** Tryptophan is cleaved at the 2,3 bond of the indole ring by IDO1, IDO2, or TDO, opening the ring and producing N-formylkynurenine, which is hydrolyzed to kynurenine. IDO1 has a low Km for tryptophan (~20 μM, comparable to plasma tryptophan), is broadly expressed under inflammatory conditions, and is the principal extra-hepatic catabolic entry. TDO has a high Km (~200 μM, well above plasma tryptophan), is expressed primarily in liver, and provides constitutive baseline kynurenine output that scales with substrate availability rather than with regulatory induction. IDO2 has a poorly characterized substrate profile and may be a partial activity backup for IDO1.

• **Branch 3 — The serotonergic pathway.** Tryptophan is hydroxylated to 5-hydroxytryptophan by TPH1 (peripheral, gut enterochromaffin cells) or TPH2 (brain, raphe nuclei), then decarboxylated to serotonin by AADC. Serotonin is further converted to N-acetylserotonin and to melatonin in pineal and extrapineal tissues. TPH2 has a Km for tryptophan of approximately 25 μM — close to the central tryptophan concentration — which is the biochemical basis for the substrate sensitivity of central 5-HT synthesis. The Km is the central observation that connects systemic tryptophan depletion to central serotonergic deficit.

• **Branch 4 — The tryptamine/decarboxylation pathway.** Tryptophan is decarboxylated directly to tryptamine by aromatic L-amino acid decarboxylase (AADC, the same enzyme used in the serotonin branch but at a different substrate selectivity) or, more substantially, by microbial tryptophan decarboxylases in the gut lumen. Tryptamine is then rapidly metabolized by

monoamine oxidase A to indole-3-acetaldehyde and further to indole-3-acetic acid, a major urinary tryptophan metabolite. Microbial tryptamine output and microbial indole-derivative output collectively constitute the gut–brain axis tryptophan signaling system, with AHR as the principal central receptor.

The partition is structured at the committed-step level by the relative Km, Vmax, and inducibility of the four entry enzymes. Under homeostatic conditions, the partition is dominated by protein synthesis (Branch 1), with kynurenine flux (Branch 2) carrying the bulk of the remaining catabolic flux at a slow constitutive rate driven by hepatic TDO, and serotonin synthesis (Branch 3) and tryptamine production (Branch 4) carrying small fractions of total flux. Under inflammatory conditions, the partition is dominated by IDO-driven kynurenine flux, which can transiently exceed protein-synthesis flux during peak immune activation and which depletes the central tryptophan pool sufficiently to substrate-limit Branch 3 and to throttle Branch 1 at tryptophan codons.

4.3 IDO Induction: The Master Switch

IDO1 is transcriptionally induced by IFN-γ acting through the JAK1/STAT1 pathway, with secondary induction by IL-1β, TNF-α, and TLR ligands. IDO1 induction is the *single* most important regulatory event in tryptophan partition because it changes the partition geometry: it adds a high-flux entry point with a Km matched to the prevailing tryptophan concentration, simultaneously increasing absolute kynurenine flux and depleting the substrate pool available to all other branches. The kinetics of IDO induction are typical of an immune-effector enzyme: protein levels rise over hours to days, peak at one to three days under sustained stimulation, and decay over similar timescales after stimulus withdrawal. Under chronic stimulation — for example, the chronic low-grade inflammation of aging, the chronic infections implicated in some AD subtypes, or the sustained microglial activation of established neurodegeneration — IDO1 expression remains elevated for years, producing a *sustained partition shift* that the homeostatic system cannot reset.

The therapeutic implication is direct: in any patient with sustained central IDO induction, the central serotonin pool will be substrate-limited regardless of SSRI use, the kynurenine pool will be elevated, the QUIN/KYNA ratio will depend on the local cellular composition (microglia vs. astrocytes), and the de novo NAD+ arm will be active but coupled to inflammatory drive. Each downstream branch therefore reads the IDO state as its upstream input.

4.4 The Integrated Stress Response and ATF4 Coupling

ATF4 is the master transcription factor of the integrated stress response, induced by phosphorylation of eIF2α through the kinases GCN2 (amino-acid deprivation), PERK (ER stress), HRI (heme deprivation), and PKR (viral RNA). Under each of these stress conditions, eIF2α phosphorylation suppresses cap-dependent translation but selectively enables ATF4 translation through upstream open reading frames, and ATF4 then drives expression of genes that include NAMPT, NMRK1, ASNS, CHOP, and — relevant to the present framework — tryptophan-pathway enzymes including TDO and several kynurenine-pathway downstream enzymes (Mungrue et al., 2009; Han et al., 2013). The ATF4 program is therefore *substrate-restoring*: it expands the pools that the stress was depleting.

The relevance to tryptophan partition is twofold. First, GCN2 senses tryptophan-codon stalling — exactly the stalling that IDO-driven tryptophan depletion would cause — and activates the ISR. The ISR then upregulates kynurenine-pathway enzymes, further committing tryptophan to the kynurenine branch. The system is therefore *positively coupled* under sustained inflammatory drive: the depletion triggers the response that deepens the depletion. Second, the ISR upregulates NAD+ salvage enzymes, but the salvage arm requires nicotinamide as substrate; under sustained PARP-1 hyperactivation (which converts NAD+ to ADP-ribose chains without returning nicotinamide to the salvage pool), the salvage arm is throttled, and the de novo arm — terminating in NAD+ via kynurenine and quinolinic acid — becomes the dominant NAD+ resupply route. The de novo arm therefore reads the same inflammatory IDO signal that depletes the serotonergic and protein-synthesis branches, but it converts that signal into NAD+ output. The de novo NAD+ arm is the only branch of the tryptophan partition for which inflammatory IDO induction is *bioenergetically restorative* rather than depleting.

4.5 The Partition as a Coupled Control System

A useful formal frame for the four branches is as a coupled control system with one shared substrate (tryptophan pool), four entry enzymes (TrpRS, IDO/TDO, TPH, AADC/microbial decarboxylases), and one principal external regulator (IFN-γ). Under homeostatic conditions, the system runs at a steady-state allocation dominated by Branch 1 with small fluxes to Branches 2–4. Under inflammatory perturbation, IFN-γ drives IDO induction, which shifts the partition toward Branch 2; the resulting tryptophan depletion is sensed by GCN2, which activates ATF4, which upregulates downstream kynurenine-pathway enzymes including those that produce NAD+. Branch 3 falls below its TPH2 Km and central 5-HT synthesis drops. Branch 1 stalls at tryptophan codons in the cells with highest IDO output (typically activated microglia and infiltrating macrophages), producing proteostatic stress and feeding back into the ISR. Branch 4 (microbial tryptamine) is regulated independently by gut microbiota composition and, under most conditions, contributes a small fraction of total flux but can be elevated under dysbiosis.

The partition is *over-determined* — multiple branches respond to the same upstream signal, and the response is asymmetric across branches. This is the formal sense in which the partition is a "node": it is the place where one upstream signal (inflammation, sensed as IFN-γ) propagates to four downstream readouts (excitotoxic signaling, NAD+ supply, serotonergic tone, proteostatic fidelity) through a single shared substrate (tryptophan). No other amino acid in mammalian biochemistry occupies a comparable position.

5. Chapter II — The Kynurenine Branch and the Excitotoxic Terminus

5.1 The Cascade

The kynurenine pathway proceeds from tryptophan through nine principal enzymatic steps. IDO/TDO cleaves the indole ring to produce N-formylkynurenine, which formamidase hydrolyzes to kynurenine. Kynurenine then has three possible fates: hydroxylation by KMO to 3-hydroxykynurenine (committing the substrate toward QUIN); transamination by KAT to kynurenic acid (committing the substrate toward KYNA); or, in a minor branch, hydrolysis by kynureninase to anthranilic acid. The 3-hydroxykynurenine intermediate is further hydrolyzed by kynureninase to 3-hydroxyanthranilic acid, which is opened by 3-hydroxyanthranilate dioxygenase to a semialdehyde that spontaneously cyclizes to quinolinic acid. Quinolinic acid is then phosphoribosylated by QPRT to nicotinic acid mononucleotide, which enters the NAD+ biosynthetic terminus characterized in Chapter III.

The branchpoint between KMO and KAT — that is, the partition of kynurenine between the QUIN-bound and KYNA-bound paths — is the central neurochemically relevant partition within the kynurenine branch. KMO and KAT differ in cellular distribution (microglia/macrophages vs. astrocytes), in subcellular localization (KMO on the outer mitochondrial membrane vs. KAT in the cytosol), in Km for kynurenine (KMO ~30 μM, KAT II ~900 μM — KMO has a far lower Km and therefore dominates under physiological kynurenine concentrations), and in inflammatory regulation (KMO is induced by IFN-γ and LPS, KAT is broadly unregulated). The kinetic and cell-type asymmetries jointly produce a strong default bias toward QUIN under inflammatory conditions, with KYNA accumulating only when KAT-expressing astrocytes are abundant, healthy, and presented with high kynurenine concentrations.

5.2 Quinolinic Acid as Excitotoxic NMDA Agonist

QUIN is a competitive NMDA receptor agonist at the glutamate-binding site, with a preference for NR2B-containing receptors. The Ki at NR2B-containing NMDA receptors is approximately 30 μM, comparable to the local QUIN concentrations achievable in inflamed microglial microenvironments under sustained IDO/KMO induction. The excitotoxic mechanism is classical: NMDA receptor activation drives calcium influx; sustained calcium elevation activates calpain, calcineurin, and the mitochondrial permeability transition pore; mitochondrial calcium overload triggers cytochrome c release and intrinsic apoptosis. The QUIN-driven excitotoxic mechanism is therefore additive with — and potentially synergistic with — glutamatergic excitotoxicity from astrocyte glutamate-uptake failure, with NMDA-receptor sensitization from extracellular Aβ oligomers, and with intracellular calcium overload from MAM dysfunction characterized in the Bioenergetic Collapse thesis. The convergence at the NMDA receptor is one of the strongest mechanistic motivations for the kynurenine-branch framing: QUIN supplies an *endogenous*, *inflammation-driven*, *substrate-tunable* NMDA agonist whose concentration scales with microglial activation.

Beyond receptor agonism, QUIN has additional toxic activities: it complexes with Fe^2+ to form pro-oxidant species; it potentiates lipid peroxidation in the presence of iron; it inhibits Complex I (additively with the Complex I inhibition reported for α-synuclein and TDP-43 in the Bioenergetic Collapse thesis); and it has been reported to enhance tau hyperphosphorylation through indirect mechanisms (Lugo-Huitrón et al., 2013). Each of these activities couples the kynurenine branch back to the bioenergetic and proteinopathy axes of the Collapse trilogy.

5.3 Kynurenic Acid as Broad-Spectrum Antagonist

KYNA antagonizes NMDA receptors at the glycine co-agonist site (Ki ~15 μM at the NR1 subunit), α7-nicotinic acetylcholine receptors (Ki ~1 μM), and AHR agonism. At physiological CNS concentrations (50–500 nM), KYNA's principal action is α7-nAChR antagonism, which depresses cholinergic transmission and is implicated in the cognitive deficits of schizophrenia (where CSF KYNA is elevated; Erhardt et al., 2017). At pathological concentrations (>5 μM in inflamed tissue), KYNA dampens NMDA receptor activity broadly and supplies neuroprotection against QUIN-driven excitotoxicity. The therapeutic significance is that KYNA is *contextually neuroprotective*: at concentrations sufficient to oppose QUIN excitotoxicity in inflammatory neurodegeneration, KYNA simultaneously depresses cholinergic transmission and may impair cognition through that mechanism. The therapeutic target is therefore not "more KYNA" in isolation but the QUIN/KYNA *ratio*, restored toward the homeostatic baseline through KMO inhibition (which preferentially reduces QUIN) rather than through KYNA augmentation alone.

5.4 Balin's Pathogen-Driven IDO Induction Model

Brian Balin and colleagues have argued for a *Chlamydia pneumoniae* etiology of AD in which chronic central infection drives sustained IDO induction in infected microglia, producing a long-duration kynurenine shift that constitutes one of the principal cytotoxic outputs of the infection (Balin et al., 2008; Hammond et al., 2010). The Balin framework names IDO, kynurenine, and quinolinic acid explicitly as effectors of pathogen-driven neurodegeneration, and the kynurenine-pathway markers in CSF and brain tissue from AD cohorts are consistent with the framework (Guillemin et al., 2005). The Balin framework is one of several pathogen-etiology models of AD (alongside *Herpes simplex* type 1, *Porphyromonas gingivalis*, spirochete, and CMV models), and the central biochemical commonality across the models is sustained microglial activation with IDO induction. Whether or not any single pathogen is causally responsible in any patient, the pathogen-etiology models converge on tryptophan partition as a final common pathway.

5.5 Cellular Geometry: Microglia, Astrocytes, and the Spatial Partition

The QUIN/KYNA balance is fundamentally spatial. Microglia express IDO1, KMO, and the downstream enzymes through 3-hydroxyanthranilate dioxygenase; they produce QUIN locally in their immediate microenvironment. Astrocytes express KAT but not KMO; they convert kynurenine to KYNA. Neurons express neither pathway robustly — they are recipients of the metabolites, not producers — and the QUIN/KYNA they encounter at NMDA and α7-nAChR receptors depends entirely on the local microglia/astrocyte composition and activity state.

In healthy adult brain, astrocytes outnumber microglia 4–10× depending on region, and the resting microglial state produces only baseline IDO expression. Under these conditions, kynurenine produced peripherally (TDO-driven, hepatic) and centrally (low microglial output) is dominantly processed by astrocytes through KAT to KYNA, producing a homeostatic neuromodulatory tone. Under microglial activation in neurodegeneration, the microglia/astrocyte balance shifts both in number (microglial proliferation and astrocyte reactive transition) and in metabolic activity (microglial KMO induction, reactive astrocyte loss of KAT activity in some phenotypes), producing the spatial double shift toward QUIN that characterizes the inflamed AD brain. The Homeostatic Microglial Collapse thesis (Gustafsson, 2026) supplies the upstream story for this shift: the loss of TGF-β/SMAD-maintained homeostatic microglial identity is the single upstream event from which all post-homeostatic phenotypes emerge, and the kynurenine-shift toward QUIN is one of the principal neurochemical consequences of that collapse.

5.6 Cross-Disease Evidence

Elevated CSF or plasma kynurenine-to-tryptophan ratios have been documented in AD (Widner et al., 2000; Guillemin et al., 2005), PD (Lim et al., 2017), HD (Stoy et al., 2005), ALS (Chen et al., 2010), major depression (Maes et al., 2011), and chronic fatigue syndrome (Castro-Marrero et al., 2019). The pattern is sufficiently broad to suggest that elevated kynurenine flux is a non-specific consequence of chronic neuroinflammation rather than a disease-specific lesion. The disease specificity, on the present framework, arises from the *downstream* consequences of the shift — which cell populations are most vulnerable to QUIN excitotoxicity, which circuits are most dependent on 5-HT modulation, which neurons are most dependent on de novo NAD+ resupply — rather than from the shift itself.

6. Chapter III — The NAD+ De Novo Branch and the Integrated Stress Response

6.1 The Two Arms of Mammalian NAD+ Biosynthesis

Mammalian cells synthesize NAD+ through three routes: the salvage arm (NAMPT converting nicotinamide to nicotinamide mononucleotide, which is adenylylated by NMNATs to NAD+); the Preiss-Handler arm (nicotinic acid, dietary niacin, converted through NAPRT and adenylylation to NAD+); and the de novo arm (tryptophan converted through the kynurenine pathway to quinolinic acid, then phosphoribosylated by QPRT to NaMN and amidated to NAD+). The relative contribution of each arm to total NAD+ flux varies by tissue, by physiological state, and by stress condition.

Under homeostatic conditions in most tissues, the salvage arm carries the bulk of NAD+ flux because it is fast, energetically cheap, and continuously fed by nicotinamide released from NAD+-consuming enzymes (sirtuins, PARPs, CD38). The de novo arm carries a small constitutive flux that scales with hepatic TDO output and dietary tryptophan availability. Under sustained NAD+ depletion — for example, PARP-1 hyperactivation from oxidative DNA damage, CD38 induction in inflammatory tissue, or sirtuin-driven NAD+ consumption in metabolic stress — the salvage arm is throttled because nicotinamide is being converted to NAD+ faster than it can be regenerated, and the de novo arm becomes proportionally more important. The de novo arm is also upregulated transcriptionally by ATF4 under integrated stress response activation, which connects the inflammatory IDO signal to NAD+ resupply through the kynurenine pathway.

6.2 The De Novo Arm Through Quinolinic Acid

The terminal four steps of the kynurenine pathway — kynurenine ☐ 3-hydroxykynurenine ☐ 3-hydroxyanthranilic acid ☐ α-amino-β-carboxymuconate-ε-semialdehyde ☐ quinolinic acid ☐ nicotinic acid mononucleotide — couple the kynurenine branch to NAD+ biosynthesis through QPRT. QPRT is the committed-step enzyme of the de novo arm and is expressed broadly, with highest expression in liver and kidney. CNS QPRT expression is regionally variable and inflammation-responsive: microglia upregulate QPRT under sustained IFN-γ stimulation, and astrocytes have lower but inducible QPRT expression. The implication is that the de novo arm is enzymatically prepared, under inflammatory conditions, to convert the same quinolinic acid that would otherwise accumulate as an excitotoxin into NAD+.

The kinetic question is whether QPRT capacity is sufficient to keep up with KMO-driven QUIN production under sustained inflammatory drive. The available evidence suggests that QPRT is rate-limiting at high QUIN flux: QPRT Vmax is moderate, QPRT is sensitive to product inhibition, and QPRT is not as strongly induced by ATF4 as the earlier kynurenine-pathway enzymes. The result is that under sustained microglial IDO/KMO induction, QUIN production exceeds QPRT capacity, QUIN accumulates as an excitotoxin, and the net contribution of the de novo arm to NAD+ supply is sub-stoichiometric to the QUIN flux generated. The kynurenine branch is therefore *bioenergetically wasteful* under inflammatory drive: it generates a high-toxicity intermediate (QUIN) at high flux and converts only a fraction of that intermediate to the useful end-product (NAD+).

6.3 PARP-1 Hyperactivation and the LC Connection

The Bioenergetic Collapse thesis identifies the locus coeruleus as the earliest known site of AD pathology and develops a model in which LC neurons fail through PARP-1 hyperactivation driven by their unique catecholamine biochemistry: noradrenaline oxidation generates reactive aldehydes that produce DNA damage; the resulting strand breaks activate PARP-1, which consumes NAD+ to synthesize poly(ADP-ribose) chains; sustained PARP-1 activity depletes the LC NAD+ pool below the threshold required to maintain OXPHOS, mitochondrial biogenesis, and the integrated stress response. The PARP*Locus*Coeruleus*Phase*I working paper (Gustafsson, 2026) develops this argument in detail and identifies ATF4-driven NAD+ salvage as the principal homeostatic counter to PARP-1 NAD+ consumption.

The tryptophan partition supplies the missing piece of the LC story. ATF4 upregulates both salvage-arm enzymes (NAMPT, NMRK1) and kynurenine-pathway enzymes in the LC and surrounding tissue. Under chronic PARP-1 drive, the salvage arm runs into nicotinamide limitation (PARP-1 polymerization sequesters nicotinamide in ADP-ribose chains rather than returning it to the salvage pool), and the de novo arm becomes the dominant NAD+ resupply route. The de novo arm requires sustained tryptophan supply through the kynurenine pathway; the tryptophan supply requires that peripheral tryptophan reach the LC microenvironment; and the IDO induction that drives kynurenine flux is itself inflammatory, propagating the microglial activation that elsewhere in the brain produces the kynurenine-branch shift toward QUIN. The LC is therefore *simultaneously* the principal site of PARP-1-driven NAD+ depletion in AD *and* the principal beneficiary of de novo NAD+ resupply through the tryptophan partition. Whether the partition delivers enough tryptophan to the LC to sustain the de novo arm under chronic PARP-1 drive is, on the present framework, the critical question that determines whether LC neurons survive or fail.

6.4 CD38, NAD+ Consumption, and the Microglial Drain

CD38 is an ectoenzyme and intracellular NAD+ glycohydrolase that is highly induced in activated microglia and infiltrating macrophages (Camacho-Pereira et al., 2016; Chini et al., 2020). CD38 is a *NAD+ consumer*, not an NAD+ producer, and CD38 induction in inflammatory microglia creates a "NAD+ sink" that drains NAD+ from the surrounding microenvironment. The Bioenergetic Collapse thesis treats CD38 as a principal contributor to microglial metabolic collapse: the same microglial activation that increases bioenergetic demand also upregulates the enzyme that depletes the cofactor required to meet that demand.

The tryptophan partition adds a further layer to the CD38 story. Microglial activation simultaneously induces IDO (driving the kynurenine shift), KMO (driving kynurenine toward QUIN), CD38 (consuming NAD+), and QPRT (resynthesizing NAD+ from QUIN). The net result depends on the relative kinetics of the four enzymes: if QPRT capacity is sufficient to consume the QUIN produced by KMO, the de novo arm can partially offset the CD38 drain; if QPRT is rate-limiting (as the evidence suggests), QUIN accumulates as an excitotoxin and the CD38 drain is largely uncompensated. The framework therefore predicts that pharmacological inhibition of KMO — which redirects kynurenine toward KAT and KYNA, reducing both QUIN excitotoxicity *and* the metabolic load on QPRT — should preserve microglial NAD+ better than direct NAD+ precursor supplementation alone, because it removes the upstream wasteful flux through QUIN.

6.5 Niacin, Tryptophan Loading, and the Pellagra Lesson

Pellagra is the original tryptophan-partition disease. The clinical syndrome — dermatitis, diarrhea, dementia — emerges when dietary niacin and tryptophan are both insufficient to maintain NAD+ pools. The dementia component is reversible by either niacin or tryptophan supplementation; the reversibility demonstrates that the cognitive deficit is a *substrate* deficit (NAD+ insufficient for normal neuronal function) rather than a *structural* deficit (mitochondrial damage, neuronal loss, proteinopathy). The lesson is that NAD+ depletion alone — without additional structural damage — produces a dementia phenotype that is clinically severe but pharmacologically reversible.

The pellagra lesson supplies a positive prediction for tryptophan-partition therapeutics in early-stage neurodegeneration: if a patient's cognitive deficits are

dominated by the NAD+-depletion component of the bioenergetic collapse (early LC dysfunction, early microglial metabolic exhaustion, but not yet substantial neuronal loss), partition restoration — through niacin, tryptophan loading, or both, combined with KMO inhibition to reduce the wasteful QUIN flux — should produce measurable cognitive improvement. The prediction is the cleanest empirical test of the partition framework available, because pellagra-grade NAD+ depletion is straightforwardly diagnosed by plasma niacin-derivative measurement, and partition-restoration interventions are already FDA-approved for unrelated indications (nicotinamide riboside as a supplement, tryptophan as a sleep aid, KMO inhibitors in clinical trials for HD).

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7. Chapter IV — The Serotonergic Branch, BDNF, and Adult Neurogenesis

7.1 The 5-HT Synthesis Bottleneck

Central serotonin synthesis is committed at TPH2, which hydroxylates tryptophan to 5-hydroxytryptophan, the rate-limiting step of the pathway. AADC then decarboxylates 5-HTP to serotonin in the same reaction step that also produces dopamine from L-DOPA in catecholaminergic neurons. TPH2 has a Km for tryptophan of approximately 25 μM, close to the central tryptophan concentration of 10–25 μM under homeostatic conditions. The Km is the central biochemical observation that connects tryptophan partition to serotonergic output: TPH2 is normally substrate-saturated, but the saturation margin is small, and small drops in central tryptophan availability produce proportional drops in 5-HT synthesis.

The serotonergic system is organized around the raphe nuclei — principally the dorsal raphe nucleus (DRN) and median raphe nucleus (MnRN) — which project to nearly all cortical and subcortical regions through diffuse, low-density axonal arborizations. Each raphe neuron makes hundreds of thousands of synaptic contacts, releasing 5-HT volumetrically rather than through discrete synaptic boutons. The system is therefore not specialized for fast, precise neurotransmission; it is a neuromodulatory system that biases the activity of broad cortical and subcortical territories. The functional consequences of 5-HT depletion are correspondingly broad: mood depression, sleep disruption, appetite changes, cognitive flexibility

deficits, and impaired adult hippocampal neurogenesis.

7.2 5-HT, BDNF, and Adult Hippocampal Neurogenesis

5-HT acts on 5-HT1A autoreceptors on raphe neurons (negative feedback) and on postsynaptic 5-HT1A, 5-HT2A, 5-HT2C, 5-HT4, and 5-HT7 receptors across the brain. In the hippocampus, 5-HT1A and 5-HT4 receptor activation increases CREB phosphorylation and BDNF expression in granule cells and pyramidal neurons. BDNF acts on TrkB receptors to support neurogenesis, dendritic growth, synaptogenesis, and synaptic plasticity. The 5-HT-to-BDNF-to-neurogenesis pathway is the principal molecular substrate of the SSRI clinical effect on depression: SSRIs increase synaptic 5-HT, 5-HT increases BDNF, BDNF supports neurogenesis, and the resulting circuit-level changes contribute to the antidepressant clinical effect (Castrén, 2014; Björkholm and Monteggia, 2016).

The link to neurodegeneration runs through adult hippocampal neurogenesis. Adult neurogenesis in the dentate gyrus subgranular zone is a documented feature of human hippocampus across the lifespan (Boldrini et al., 2018, with some controversy regarding magnitude), and its decline is associated with cognitive aging and is reduced in AD (Tobin et al., 2019). The Convergent Synaptic Collapse thesis treats adult neurogenesis as one of the principal substrates of cognitive resilience: hippocampal circuits with active neurogenesis maintain pattern-separation capacity and resist the cognitive collapse that would otherwise follow synaptic damage. The 5-HT-BDNF axis is the principal trophic input to adult hippocampal neurogenesis, and tryptophan partition determines the 5-HT supply on which the axis depends.

The framework therefore makes a sharp prediction: chronic inflammatory IDO induction should produce *progressive impairment of adult hippocampal neurogenesis* through serotonergic withdrawal, and this impairment should precede and contribute to cognitive decline. The prediction is consistent with the late-life depression / dementia association (chronic IDO induction produces depressive symptoms first, neurogenic impairment over a longer timescale, and cognitive decline last), and it predicts that interventions that restore 5-HT availability — but only when tryptophan substrate is sufficient — should preserve neurogenesis and delay cognitive decline.

7.3 The SSRI Problem and the Partition Interpretation

SSRI clinical trials in AD have produced mixed results. Citalopram and escitalopram have shown some signal in reducing agitation in moderate AD (Porsteinsson et al., 2014), and observational studies suggest SSRI use may be associated with reduced AD progression (Cirrito et al., 2011; Bartels et al., 2018). But SSRIs have not produced robust disease-modifying effects in AD trials, and the discrepancy between the strong mechanistic rationale (5-HT supports neurogenesis, BDNF expression, and Aβ clearance through HTR4 activation) and the modest clinical effect requires explanation.

The partition framework supplies one. SSRIs act by blocking the serotonin reuptake transporter, increasing the concentration of 5-HT in the synaptic cleft. The mechanism requires that 5-HT *be present* in the synapse to begin with — that is, it requires that the raphe neurons have synthesized 5-HT and released it. If tryptophan partition has been substantially shunted to the kynurenine branch by sustained IDO induction, central tryptophan availability falls below the TPH2 Km, 5-HT synthesis drops, and the synaptic 5-HT that SSRIs would amplify is reduced at source. The SSRI mechanism is therefore *uncoupled from substrate availability*: it amplifies whatever 5-HT signal exists but cannot increase the synthesis rate of 5-HT under substrate limitation.

The prediction is that SSRI efficacy in AD should correlate with the plasma kynurenine-to-tryptophan ratio: patients with low ratios (intact tryptophan partition) should respond to SSRIs because their 5-HT synthesis is not substrate-limited, while patients with high ratios (shunted partition) should not respond because their 5-HT synthesis is substrate-limited and SSRIs cannot rescue it. The further prediction is that *combined* SSRI + tryptophan-loading therapy should rescue the response in shunted patients, and that *combined* SSRI + KMO inhibitor therapy should also work — both by restoring tryptophan availability at TPH2. To my knowledge, neither combination has been systematically tested in AD or in late-life depression, and the framework identifies them as a high-priority therapeutic axis.

7.4 Melatonin: The Pineal Branch

5-HT is the substrate for melatonin synthesis in the pineal gland through N-acetylation (AANAT) and O-methylation (ASMT). Melatonin synthesis is therefore the *third tier* of tryptophan partition: tryptophan to 5-HTP to 5-HT to melatonin. The pineal-melatonin output is circadian and is regulated by suprachiasmatic input rather than by substrate availability, but the substrate availability does bound the achievable melatonin peak. Melatonin is a potent antioxidant, supports mitochondrial function, and has been investigated as a neuroprotective intervention in AD with mixed results (Cardinali et al., 2010; Wade et al., 2014). The framework treats melatonin as a downstream node of the partition with its own neuroprotective relevance, and predicts that the same partition shifts that withdraw 5-HT substrate also withdraw melatonin substrate, producing parallel deficits in mood, sleep, and oxidative defense — all of which are observed early in AD progression.

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8. Chapter V — The Tryptamine Branch, TrpRS Inhibition, and the Gut–Brain Proteostasis Axis

8.1 Microbial Tryptophan Metabolism

The gut microbiota consumes a fraction of dietary tryptophan before host absorption, producing indole, indole-3-acetate, indole-3-propionate, indole-3-aldehyde, tryptamine, and other indoleamines. The principal microbial enzymes are tryptophanase (producing indole) and tryptophan decarboxylase (producing tryptamine), expressed broadly across commensal *Lactobacillus*, *Bifidobacterium*, *Clostridium*, and other gut taxa. The output is highly diet- and microbiota-composition-dependent, with vegetarian and high-fiber diets producing different tryptophan-derivative profiles than Western diets, and antibiotic-induced dysbiosis dramatically altering output (Roager and Licht, 2018).

The principal central reception of microbial tryptophan derivatives is through the aryl hydrocarbon receptor (AHR), which is expressed in microglia, astrocytes, neurons, intestinal epithelium, and peripheral immune cells. AHR ligands modulate immune tone, microglial state, and barrier integrity at the gut and at the BBB. The peripheral microbial branch of the tryptophan partition is therefore *immunomodulatory*: it does not directly compete with the central serotonergic or

kynurenine branches, but it shapes the inflammatory tone that regulates IDO induction, which then shapes the partition itself. The microbial branch is the *exogenous regulator* of the central partition.

8.2 Paley's Tryptamine–TrpRS Framework

Paley (2019, 2024) has developed a framework in which microbiota-derived tryptamine, absorbed from the gut and reaching the brain through the portal-systemic circulation, competitively inhibits tryptophanyl-tRNA synthetase (TrpRS) and corrupts the first step of protein biosynthesis at tryptophan codons. On Paley's account, the resulting misfolded or incomplete translation products at tryptophan-rich positions are the proteomic substrate from which Aβ, tau, α-synuclein, and other aggregation-prone proteins arise. The framework is bold: it places the principal etiologic mechanism of AD and related proteinopathies in the gut microbiome, with the central proteinopathy as a downstream consequence of peripheral aminoacylation interference.

The direct experimental evidence for the framework is limited. TrpRS does have substrate-recognition residues that can interact with tryptophan analogs, but the affinity of tryptamine for TrpRS at physiological tryptamine concentrations (~10–100 nM in plasma, somewhat higher in portal circulation) is below the affinity of tryptophan itself (~5–10 μM intracellular concentration, well above the TrpRS Km). For tryptamine to compete effectively at TrpRS would require concentrations substantially higher than those reported in vivo, or a localization effect that concentrates tryptamine at TrpRS-containing subcellular compartments. The framework is therefore mechanistically plausible but quantitatively uncertain, and the present dissertation treats it as a candidate fifth branch of the partition rather than as an established one.

8.3 Implications Even If Paley's Specific Mechanism Is Wrong

Whether or not tryptamine specifically inhibits TrpRS in vivo, the gut–brain tryptophan axis is relevant to the partition framework through several robust mechanisms. First, microbial tryptophan consumption directly reduces host tryptophan absorption, lowering the substrate pool for both the kynurenine and serotonergic branches. Second, microbial indole-derivative output modulates AHR signaling, which regulates IDO expression and therefore the partition itself. Third, microbial dysbiosis is associated with increased peripheral inflammation, which through IFN-γ drives IDO induction. Fourth, gut barrier dysfunction (leaky gut) increases circulating LPS, which activates TLR4 on peripheral and central immune cells, producing inflammatory drive that intersects the tryptophan partition through the IDO pathway. The microbial branch is therefore relevant to the partition through at least four independent mechanisms, and any framework that ignores it under-specifies the partition's regulatory inputs.

8.4 Connection to the Proteinopathy Axes

The Convergent Synaptic Collapse thesis identifies Aβ and tau as principal effectors of synaptic pathology in AD, and the Bioenergetic Collapse thesis treats them as mitochondrial toxins. Both treatments take the proteins themselves as given — that is, they characterize what the misfolded proteins do once they exist, but they do not address what causes the misfolding rate to increase with age. The Paley framework, even if its specific TrpRS mechanism is uncertain, supplies a candidate upstream explanation: age-related changes in gut microbiota composition, combined with age-related impairment of host clearance of microbial metabolites, produce a chronic low-grade substrate-handling perturbation at protein synthesis that increases the misfolding rate at tryptophan codons. The framework also predicts that interventions that restore microbial composition (probiotics, fermented foods, fecal microbiota transplant) should reduce the substrate-handling perturbation and slow proteinopathy progression — predictions that are being tested in early-phase trials (Vogt et al., 2017; Marizzoni et al., 2020).

9. Chapter VI — Partition Dynamics: The Inflammatory Shunt and Its Consequences

9.1 The Inflammatory Shunt, Formally Stated

The central claim of the present thesis can be stated formally as follows. The tryptophan partition has four committed-step enzymes (TrpRS, IDO/TDO, TPH, AADC/microbial decarboxylases) and one shared substrate pool (free intracellular tryptophan). Under homeostatic conditions, the partition runs at an allocation dominated by Branch 1 (protein synthesis) with small fluxes to Branches 2–4. Under inflammatory stimulation (IFN-γ, IL-1β, TLR ligands, sustained microglial activation), the IDO/TDO entry enzyme of Branch 2 is transcriptionally induced, increasing its Vmax by an order of magnitude or more. Because IDO has a Km for tryptophan (~20 μM) that is at or below the substrate concentration, the increased Vmax translates directly into increased flux. The increased flux into Branch 2 reduces the shared substrate pool, which:

- Reduces TPH2 activity in Branch 3 because TPH2 Km is at the substrate concentration, producing a roughly proportional reduction in central 5-HT synthesis.
- Reduces TrpRS activity in Branch 1 at the high-IDO cells (microglia, infiltrating macrophages), producing tryptophan-codon translation stalling that activates GCN2 and the integrated stress response.
- Drives downstream kynurenine flux through KMO toward 3-hydroxykynurenine and quinolinic acid; the QPRT capacity is partially sufficient to convert QUIN to NaMN for de novo NAD+ synthesis, but a substantial fraction of QUIN accumulates as an excitotoxin in the inflamed microenvironment.
- Activates the ISR (through GCN2), which upregulates further kynurenine-pathway enzymes and salvage-arm NAD+ enzymes, partially restoring NAD+ supply but at the cost of further committing tryptophan to Branch 2.

The net effect is a *coupled shift* of the entire partition: increased kynurenine flux, decreased 5-HT synthesis, partial NAD+ restoration through the de novo arm, accumulating QUIN excitotoxicity, and proteostatic stress at tryptophan-rich loci. The shift is *sustained* under chronic inflammation because the IDO induction is

sustained, and the ISR is *self-reinforcing* under sustained tryptophan limitation because the response is precisely calibrated to deepen the limitation that activated it.

9.2 Cell-Type-Specific Vulnerability

The partition shift falls unequally across cell types. Cells with high constitutive 5-HT synthesis (raphe neurons) experience the most severe substrate withdrawal from Branch 3. Cells with high NAD+ consumption (LC neurons, activated microglia) experience the most severe demand on de novo NAD+ resupply through the kynurenine arm. Cells with high protein synthesis rates (rapidly dividing or strongly transcribing cells) experience the most severe TrpRS substrate limitation. Cells with high NMDA receptor density (PV+ interneurons, hippocampal pyramidal neurons in CA1) experience the most severe QUIN-driven excitotoxicity.

The cell-type vulnerability profile produced by sustained inflammatory partition shift is therefore: raphe-driven 5-HT depletion (mood, neurogenesis, BDNF), LC-driven NAD+ depletion (bioenergetic collapse, ISR exhaustion), CA1 and PV+ interneuron QUIN excitotoxicity (memory, gamma rhythms), and selective translation impairment at tryptophan-rich loci (proteostasis). The profile maps with surprising completeness onto the early-AD vulnerability profile: raphe and LC are among the earliest sites of AD pathology; PV+ interneurons and CA1 pyramidal neurons are among the earliest cellular targets; and proteostatic stress is a near-universal feature of the disease. The mapping is, on the present framework, not coincidental — it is the predicted output of sustained inflammatory partition shift.

9.3 The Cognitive Reserve / Resilience Reading

A long-standing puzzle in AD epidemiology is the *cognitive reserve* phenomenon: individuals with comparable plaque and tangle burden differ substantially in clinical expression of dementia, and some heavily pathologically affected individuals remain cognitively intact through life (Stern, 2012; SantaCruz et al., 2011). The cognitive reserve / resilience literature has identified educational attainment, social engagement, and physical activity as protective factors without supplying a unifying mechanistic account.

The partition framework supplies a candidate account. Cognitive resilience may reflect preserved tryptophan partition under conditions of comparable inflammatory drive: individuals whose partition has not been heavily shunted toward the

kynurenine branch retain their serotonergic capacity, retain their de novo NAD+ capacity, retain their proteostatic fidelity, and resist the QUIN excitotoxicity that the same brain pathology would otherwise drive. The protective factors identified epidemiologically — education, social engagement, physical activity — are each plausibly anti-inflammatory in mechanism, and each plausibly preserves partition function. The framework therefore predicts that resilience should correlate with the plasma kynurenine-to-tryptophan ratio and with the QUIN/KYNA ratio in CSF, and that interventions that reduce systemic inflammation should preserve cognitive function even in the absence of plaque or tangle clearance.

9.4 The Age Trajectory of the Partition

Plasma tryptophan declines slowly with age in most adult cohorts, and the plasma kynurenine-to-tryptophan ratio rises slowly with age, reflecting the chronic low-grade inflammation of aging (Frick et al., 2004; Theofylaktopoulou et al., 2013). The ratio rises faster in individuals who develop dementia than in cognitively intact aged controls, but the difference is not large and the temporal precedence is hard to establish from cross-sectional data. Prospective cohorts with serial tryptophan and kynurenine measurements over decades have not been systematically reported, and the present framework predicts that such cohorts would show progressive partition shift over years to decades in pre-clinical AD, with the QUIN/KYNA ratio rising in CSF and the plasma kynurenine-to-tryptophan ratio rising peripherally years before measurable cognitive decline. The prediction is testable in existing biobank cohorts with stored plasma and CSF samples at multiple timepoints.

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10. Chapter VII — Therapeutic Implications and Experimental Predictions

10.1 The Therapeutic Surface

The tryptophan partition framework supplies a cross-cutting therapeutic surface organized around three intervention classes:

Class A — Entry-enzyme modulation. IDO inhibitors (epacadostat, indoximod, navoximod — developed for oncology and immune modulation) and TDO inhibitors (LM10, 680C91 — earlier-stage) reduce the upstream commitment of

tryptophan to the kynurenine branch. The framework predicts that IDO inhibition should reduce kynurenine flux, increase central tryptophan availability, restore 5-HT synthesis, reduce QUIN excitotoxicity, and reduce CD38-coupled NAD+ drain — that is, it should *globally restore* partition function. The clinical evidence in oncology is that IDO inhibition is well-tolerated and produces measurable changes in plasma kynurenine-to-tryptophan ratios; the question for neurodegeneration is whether central IDO can be inhibited without disrupting peripheral immune tolerance to an extent that produces autoimmune side effects.

Class B — Mid-pathway redirection. KMO inhibitors (CHDI-340246, JM6, and others — developed principally for HD) redirect kynurenine flux from the QUIN-bound path toward KAT-mediated KYNA production. The framework predicts that KMO inhibition should reduce QUIN excitotoxicity, increase KYNA neuroprotection, and reduce the wasteful QPRT-bound flux that under sustained microglial activation exceeds QPRT capacity. KMO inhibition does not restore tryptophan availability to the serotonergic or protein-synthesis branches — it only redirects the kynurenine flux that has already been committed — but it does convert the kynurenine branch from a *net excitotoxic* to a *net neuroprotective* configuration. The clinical evidence in HD is encouraging at the biomarker level; clinical efficacy data are still developing.

Class C — Downstream substrate restoration. Nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN) supply NAD+ precursors through the salvage and Preiss-Handler arms, bypassing the de novo arm entirely. Tryptophan supplementation supplies upstream substrate to all four branches simultaneously, raising central tryptophan availability for 5-HT synthesis, protein synthesis, and kynurenine flux. SSRIs amplify 5-HT signaling at the synapse, partially compensating for reduced 5-HT synthesis under substrate limitation.

The framework predicts that the optimal therapeutic regimen for a patient with substantial partition shift is *combination therapy* across classes: IDO inhibition (Class A) to reduce upstream shunt, KMO inhibition (Class B) to redirect committed kynurenine flux, and NAD+ precursor / tryptophan loading (Class C) to restore substrate pools and to support the bioenergetic and serotonergic branches. Monotherapy at any single target leaves the other branches uncorrected. The prediction is testable in early-phase neurodegeneration trials with combination arms.

10.2 Predicted Biomarkers

The framework generates a specific biomarker panel for tryptophan partition assessment:

- **Plasma tryptophan, kynurenine, kynurenic acid, 3-hydroxykynurenine, quinolinic acid** — direct partition flux readouts.
- **Plasma kynurenine-to-tryptophan ratio** — the canonical inflammatory IDO induction marker.
- **CSF QUIN/KYNA ratio** — the central excitotoxic-vs-neuroprotective partition readout.
- **Plasma 5-HIAA (5-hydroxyindoleacetic acid)** — central serotonergic output proxy.
- **Plasma NAD+ and NAD+/NADH ratio** — bioenergetic terminus readout.
- **Plasma indole, indole-3-acetate, indole-3-propionate** — microbial branch readout.
- **CSF IL-6, IFN-γ, IL-1β** — upstream inflammatory drive readouts.

The panel is operationalizable in current clinical laboratories with mass spectrometry methods that are already standard for amino acid and neurochemical metabolomics. The framework predicts that the panel should track disease state, predict progression rate, and identify subpopulations most likely to respond to specific partition-restoration interventions.

10.3 Falsifiable Experimental Predictions

The framework generates seven specific predictions that are falsifiable with currently available experimental and clinical methods:

Prediction 1 (Cross-sectional). Plasma kynurenine-to-tryptophan ratio should correlate negatively with cognitive function in aged cohorts, after controlling for age, education, and APOE genotype. *Falsification:* No correlation, or positive correlation, in a large cohort with rigorous cognitive testing.

Prediction 2 (Longitudinal). In prospective cohorts followed from cognitively intact baseline, rising kynurenine-to-tryptophan ratios should predict subsequent cognitive decline with a lead time of years. *Falsification:* No predictive association, or association only after cognitive decline is already established.

Prediction 3 (Spatial). In post-mortem AD brain, CSF and brain-tissue QUIN/KYNA ratios should be elevated specifically in regions of greatest microglial activation, and the elevation should correlate with PV+ interneuron loss and gamma-rhythm disruption. *Falsification:* Uniform QUIN/KYNA elevation across regions, or no correlation with regional microglial or interneuron pathology.

Prediction 4 (Therapeutic, KMO). KMO inhibition in early-AD patients should reduce CSF QUIN, increase CSF KYNA, reduce CSF NfL (neurodegeneration biomarker), and produce measurable cognitive stabilization over 12–24 months. *Falsification:* No biomarker change, or biomarker change without clinical benefit.

Prediction 5 (Therapeutic, IDO). IDO inhibition in early-AD patients should produce a global partition restoration — reduced kynurenine-to-tryptophan ratio, increased plasma 5-HIAA, increased plasma NAD+ — and a clinical benefit larger than either KMO inhibition or NAD+ precursor supplementation alone. *Falsification:* Either no clinical benefit, or autoimmune toxicity that prevents central efficacy assessment.

Prediction 6 (Therapeutic, SSRI interaction). SSRI clinical response in AD-related agitation, depression, or cognitive decline should correlate negatively with baseline plasma kynurenine-to-tryptophan ratio: patients with high ratios should respond poorly because their 5-HT synthesis is substrate-limited. *Falsification:* SSRI response is independent of partition status, or correlates positively with kynurenine-to-tryptophan ratio.

Prediction 7 (Combination therapy). A factorial trial comparing (a) IDO inhibition alone, (b) KMO inhibition alone, (c) NAD+ precursor alone, (d) all three in combination, (e) placebo, in early-AD patients should show that the combination arm produces a clinical benefit substantially larger than any monotherapy arm. *Falsification:* Combination produces no benefit beyond best monotherapy, or combination produces toxicity that exceeds clinical benefit.

The seven predictions are not equally easy to test, but each is operationalizable with current methods, and each would substantially constrain the framework's claims if it failed. The framework is therefore properly falsifiable in the Popperian sense — its central claims make testable, risky predictions that can be checked against future data.

10.4 Connection to the Collapse Trilogy

The therapeutic implications of the partition framework intersect each axis of the Collapse trilogy. The Convergent Synaptic Collapse thesis identifies PV+ interneuron protection, perineuronal net stabilization, and gamma-frequency restoration as therapeutic priorities. The partition framework adds: KMO inhibition reduces QUIN-driven NMDA excitotoxicity at PV+ interneurons; restored serotonergic tone supports BDNF-mediated synaptic resilience; restored NAD+ supply supports gamma-frequency firing demands. The Homeostatic Microglial Collapse thesis identifies the loss of TGF-β/SMAD-maintained homeostatic microglial identity as the upstream event in microglial pathology. The partition framework adds: IDO induction in activated microglia is one of the principal effectors of homeostatic-state failure, and IDO inhibition combined with anti-inflammatory interventions may help preserve the homeostatic signature. The Bioenergetic Collapse thesis identifies mitochondrial quality-control failure and NAD+ depletion as central. The partition framework adds: the de novo NAD+ arm through tryptophan is the principal stress-response NAD+ resupply route, and its capacity is limited by upstream IDO/KMO competition for tryptophan substrate.

The partition framework is therefore *not a competitor* to the Collapse trilogy's three axes; it is a *substrate framework* that supplies the common metabolic coupling across the three. The trilogy's mechanistic claims at each axis remain intact; the partition adds the metabolic accounting that links them.

11. Conclusion

This dissertation has argued that tryptophan is the single amino acid whose catabolism opens onto four mechanistically distinct branches relevant to neurodegeneration — kynurenine, NAD+ de novo synthesis, serotonin, and tryptamine — and whose partition across those branches is itself a disease-relevant, inflammation-regulated variable. The partition is coupled to the Collapse trilogy's three axes through specific molecular mechanisms: kynurenine-branch QUIN drives excitotoxicity at the synaptic axis; the NAD+ de novo branch supports the bioenergetic axis; serotonergic withdrawal impairs adult neurogenesis and BDNF signaling that protect against synaptic loss; and inflammatory IDO induction is itself a hallmark of microglial homeostatic-state failure. The framework explains a set of otherwise disparate clinical observations — the late-life depression / dementia association, the SSRI failure in AD, the pellagra-dementia precedent, the chronic-infection / dementia association — through a single metabolic mechanism, and it generates specific, falsifiable predictions that distinguish it from alternative frameworks.

The framework does not displace the existing trilogy. It supplies the missing metabolic accounting that connects the three axes to each other through a single shared substrate. The therapeutic implications — combination IDO/KMO inhibition with NAD+ precursor and tryptophan substrate restoration — are clinically tractable and testable in early-phase trials. The central prediction is that partition restoration in early-stage neurodegeneration, before substantial neuronal loss has occurred, should produce measurable cognitive stabilization or improvement; the partition is therefore not only a mechanistic synthesis but a candidate disease-modifying axis.

The historical anchor for the framework is pellagra: a tryptophan-partition disease with reversible dementia, whose prevention by niacin or tryptophan supplementation demonstrated a century ago that NAD+-depletion-driven cognitive failure is *substrate-correctable*. The thesis here is that the dementias of neurodegeneration may share, in their early stages, more of pellagra's reversibility than is commonly recognized — provided the partition is restored before the structural damage of advanced disease has accumulated.

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