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THE ROLE OF NEUROIMMUNE AND NEUROENDOCRINE INTERACTIONS IN ACTIVATING THE KYNURENINE PATHWAY IN STRESS RESPONSE

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A variety of regulatory systems are implicated in the stress reactions of the human body. One of the most significant is the hypothalamic-pituitary-adrenal (HPA) axis and the neuroimmune system. As energy requirements increase substantially during an immune response and the stress reaction, these two processes interact within the kynurenine pathway, which is the main pathway for tryptophan metabolism in generating cellular energy (Savitz, 2020; Murata, 2026). Cortisol, which is the end product of the HPA axis and proinflammatory cytokines such as interferon-gamma and tumor necrosis factor-alpha, are the regulators of the stress response system. The imbalance in the interaction of these two processes is a contributor to the causation of neuropsychiatric and neurodegenerative diseases (Bertollo et al, 2025; Youn at al., 2026).

This study aims to gather data on how the neuroendocrine and neuroimmune systems interact to regulate the kynurenine pathway, with the resulting in metabolic and neurophysiological changes, and their implications in sickness.

Methodology. Fifteen research articles PubMed, ScienceDirect, and SpringerLink databases containing peer-reviewed publications from 2000 to 2026 were reviewed based on their study on HPA axis, sympathetic nervous system, inflammatory cytokines, and kynurenine pathway metabolites (tryptophan, kynurenine, kynurenic acid, and quinolinic acid) in healthy and diseased conditions.

Results and Discussion. Stress produces two signals that trigger the kynurenine pathway (KP): cortisol causes the liver to produce tryptophan 2,3-dioxygenase (TDO), while pro-inflammatory cytokines like interferon-gamma and tumor necrosis factor-alpha cause the brain and peripheral organs to produce indoleamine 2,3-dioxygenase (IDO). Tryptophan is driven by these signals to produce kynurenine and not serotonin. Through increased kynurenine 3-monooxygenase (KMO) activity, the balance shifts further toward neurotoxic KP metabolites in chronically stressful situations (Bertollo et all, 2025). This results in an increase in quinolinic acid (QUIN), a potent N-methyl-D-aspartate (NMDA) receptor agonist, and 3-hydroxykynurenine (3-HK), which produces free radicals, while neuroprotective kynurenic acid (KYNA), an NMDA receptor antagonist, decreases. Through glucocorticoid resistance and sustained cortisol elevation, which cause persistent KP activation and neuroinflammation, this imbalance has been directly linked to treatment-resistant depression (Bose et al., 2026). Meta-analyses have also shown that immune activation with interferon-alpha acutely decreases tryptophan while increasing kynurenine and depression scores, providing further evidence that immunologically mediated KP shifts cause depressive symptoms (Hunt et al., 2020). Schizophrenia is characterized by an increase in central KYNA from astrocytic metabolism. This is a result in NMDA receptor hypofunction on GABA-ergic interneurons, disinhibiting glutamatergic projections and dysregulating dopaminergic systems (O'Farrell & Harkin, 2017; Savitz, 2020). This has been confirmed by post-mortem examinations and genetic correlations, which show that people with psychosis have higher levels of frontal cortex KYNA and genetic variations of KMO (Savitz, 2020). Both neurodegenerative illnesses and mood disorders are thought to be influenced by QUIN's excitotoxicity and reduced neuroplasticity.

Conclusion. The kynurenine system has been demonstrated to function as a nexus through which stress signals are received from the endocrine and immune systems. Prolonged periods of stress can induce deleterious changes within the neuroimmune and neuroendocrine systems. These changes have been implicated in the pathophysiology of depression and other brain diseases, which can be associated with the stress. The employment of pharmaceutical interventions that either target the NMDA receptors or the activity of the KMO are potential therapeutic targets to alleviate stress and neuroinflammation within the body.