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The Kynurenine Pathway: Towards Metabolic Equilibrium

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Metabolism of tryptophan along the kynurenine pathway yields multiple metabolites that collectively exhibit both a rich pharmacology and broad neurobiological significance (Schwarcz et al., 2012). This includes not just neurotoxic and neuroprotective metabolites that exert their influence via opposing action at NMDA receptors but also molecules with activity at metabotropic glutamate receptor subtypes, the aryl hydrocarbon receptor and specific G-protein coupled receptors (GPCRs) (Stone et al., 2013). Despite the therapeutic possibilities arising from this extensive pharmacological repertoire, kynurenines have struggled to reach equitable status in the scientific consciousness with other tryptophan metabolites such as serotonin and melatonin. The growing realisation that the sphere of influence of dysregulated metabolism extends to most fundamental aspects of brain function with manifestations possible across the life span has seen this imbalance somewhat rectified. Now that these metabolites are no longer neglected, it is not surprising that altered metabolism along this pathway has been associated with numerous psychiatric and neurological disorders. Indeed, the immunoresponsive and stress-reactive nature of kynurenine pathway enzymes has stimulated biomarker studies and brought into focus a number of appealing therapeutic targets of relevance across a wide swathe of pathologies. The pathway still holds much covert potential, however. Although there is now a solid grasp of several of its features and nuances, some metabolites and enzymes are still understudied. It is easy to predict that ongoing research will reveal new layers of complexity and provide fresh insights.

This Special Issue of *Neuropharmacology* is an effort to provide a collection of articles to illustrate the research challenges and opportunities provided by our mounting but still incomplete knowledge of kynurenine pathway metabolism. Schwarcz and Stone (Schwarcz and Stone, 2016) chart the rise of the kynurenines from relative obscurity to their current prominence. This overview also illuminates the knowledge gaps to be bridged, and the pitfalls and promise inherent in this complex area of research. Clearly, an understanding of kynurenine pathway metabolism is contingent on a solid appreciation of the factors influencing the availability of tryptophan under both normal and pathological conditions (Badawy, 2015). Fujigaki and colleagues (Fujigaki et al., 2016) further elaborate on the mechanisms that regulate the expression and activity of pathway enzymes, with an emphasis on cell-type specific features of the metabolic cascade.

The implications of altered metabolism of tryptophan along the kynurenine pathway are manifold and may manifest across the life span. Notarangelo and Pocivavsek (Notarangelo and Pocivavsek, 2016) emphasise the important role of fluctuations in these neuroactive metabolites during critical neurodevelopmental windows, visible particularly in cognitive impairments expressed in adulthood following kynurenic acid modulation during gestation or postnatally. The role of the immune system in activating kynurenine pathway metabolism has implications for numerous disorders, particularly when viewed through the lens of infection-mediated alterations in behaviour and the links between immune system malfunction and psychopathology (Erhardt et al., 2017; Strasser et al., 2016). Equally, activation of the kynurenine pathway by glucocorticoids is an important factor for many stress-related disorders (O'Farrell and Harkin, 2015). The possibility that kynurenine pathway metabolism could be implicated as a neurobiological factor underpinning suicidality has also received attention (Bryleva and Brundin, 2016). Finally, it is important to bear in mind that some kynurenines participate in redox reactions, and this may have repercussions for critical biological functions that malfunction in relevant pathologies (Gonzalez Esquivel et al., 2016).

As research advances in this area and moves beyond more general concepts of pathway activation, it is clear that certain metabolites of the kynurenine pathway may hold special relevance for specific disorders. For example, research now associates the accumulation of quinolinic acid with amyotrophic lateral sclerosis (ALS) (Lee et al., 2016). In tandem, information about an expanding range of molecular targets continues to emerge for previously understudied metabolites including cinnabarinic acid as an orthosteric agonist of mGlu4 receptors and the activation of mGlu2 and mGlu3 receptors by xanthurenic acid (Fazio et al., 2016). Given the important role of metabotropic glutamate receptors in the CNS as well as in peripheral and non-neural tissues, this is an especially promising avenue of investigation (for review see: (Julio-Pieper et al., 2011).

These and other developments highlighting the therapeutic potential of targeting kynurenine pathway metabolism have encouraged evaluation of the kynurenine pathway in other neurological disorders such as multiple sclerosis as well as HIV-associated neurocognitive disorders (Lovelace et al., 2016). The CNS impact of parasitic diseases, such as malaria and toxoplasmosis, has also been considered in the context of their impact on kynurenine production (Hunt et al., 2016), and exciting emerging research supports a role for the gut microbiota in the regulation of kynurenine pathway metabolism (Kennedy et al., 2016).

Taken together, the breadth of these topics should make clear our motivation to put the kynurenine pathway under the spotlight in this Special Issue. The capacity of the kynurenines to surprise us should not be underestimated, and we hope that the insights in this compilation of articles will provide both stimulus and direction for ongoing research efforts and new researchers in the field. Now that consequences of the dysregulation of kynurenine pathway metabolism is more fully appreciated, and as the range of activity of the kynurenines is further teased apart, we can start to envisage the benefits of interventions that move us back towards metabolic equilibrium.

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