The kynurenine pathway and the brain: challenges, controversies and promises

Robert Schwarcz[1] and Trevor W. Stone[2]

[1]Maryland Psychiatric Research Center, Department of Psychiatry, University of Maryland School of Medicine, Baltimore, Maryland (USA)

[2]Institute of Neuroscience and Psychology, College of Medical, Veterinary and Life Sciences, University of Glasgow, Glasgow (UK)

Abstract

Research on the neurobiology of the kynurenine pathway has suffered years of relative obscurity because tryptophan degradation, and its involvement in both physiology and major brain diseases, was viewed almost exclusively through the lens of the well-established metabolite serotonin. With increasing recognition that kynurenine and its metabolites can affect and even control a variety of classic neurotransmitter systems directly and indirectly, interest is expanding rapidly. Moreover, kynurenine pathway metabolism itself is modulated in conditions such as infection and stress, which are known to induce major changes in well-being and behaviour, so that kynurenines may be instrumental in the *etiology* of psychiatric and neurological disorders. It is therefore likely that the near future will not only witness the discovery of additional physiological and pathological roles for brain kynurenines, but also ever-increasing interest in drug development based on these roles. In particular, targeting the kynurenine pathway with new specific agents may make it possible to *prevent* disease by appropriate pharmacological or genetic manipulations.

The following overview focuses on areas of kynurenine research which are either controversial, of major potential therapeutic interest, or just beginning to receive the degree of attention which will clarify their relevance to neurobiology and medicine. It also highlights technical issues so that investigators entering the field, and new research initiatives, are not misdirected by inappropriate experimental approaches or incorrect interpretations at this time of skyrocketing interest in the subject matter.

The early days

The kynurenine pathway, which is initiated by the oxidative metabolism of tryptophan, has been studied in some detail since the early part of the twentieth century. It was originally viewed primarily as the synthetic route to nicotinamide and hence nicotinamide adenine dinucleotide (NAD⁺), a crucial co-factor for a wide range of enzymes. The kynurenine pathway formed an intriguing link between the dietary availability of vitamin B6 and tryptophan metabolism (see Badawy, 2016) since many of the major enzymes in the cascade were B6-dependent, and B6 deficiency was usefully characterised by the increased excretion of xanthurenic acid in the urine (Bender et al., 1990). No specific neurobiological activity was demonstrated for kynurenine and its catabolic products until (Lapin, 1978) showed that several tryptophan metabolites could produce convulsions when injected directly into the brain. A number of publications had earlier reported abnormal concentrations of kynurenine in various brain disorders, although those results were interpreted in terms of their effects on tryptophan and serotonin levels (Curzon, 1969; Dewhurst, 1970; Wood et al., 1978).

By the mid-1970s, reports began to appear in support of the notion that glutamate, a simple amino acid, was likely to be an excitatory neurotransmitter in the central nervous system (CNS) (Stone, 1973, 1976). Furthermore, the use of selective antagonists to block synaptic excitation suggested the existence of more than one subtype of glutamate receptors (Davies et al., 1979; McLennan, 1983). It was during a screen of several dozen newly synthesised compounds that *agonist* activity was detected in one of them. This compound, pyridine-2,3-dicarboxylic acid, also named quinolinic acid and long known as a major component of the kynurenine pathway, produced an increase in neuronal firing rate in the rat cerebral cortex (Perkins and Stone, 1983b; Stone and Perkins, 1981). Neuronal excitation was blocked by 2-amino-5-phosphonopentanoic acid (AP5), a compound reported earlier the same year to block those glutamate receptors that were selectively sensitive to N-methyl-D-aspartate (NMDA) (Davies et al., 1981; Perkins et al., 1982; Perkins et al., 1981). Thus, quinolinic acid was identified as an endogenous, selective agonist at NMDA receptors (Stone and Perkins, 1981).

NMDA was already known to produce axon-sparing, "excitotoxic" loss of neurons in the CNS (Schwarcz et al., 1978), leading to the suggestion that an overexcitation of NMDA receptors might play a key role in the aetiology of neurodegenerative disorders such as Alzheimer's disease or Huntington's disease (HD), as well as epilepsy and stroke (Schwarcz and Meldrum, 1985). In line with its ability to act as a NMDA receptor agonist, quinolinic acid was also found to cause excitotoxic neuronal lesions, which could be prevented by the selective NMDA receptor antagonist 2-amino-7-phosphonoheptanoic acid (AP7) (Foster et

al., 1983). As a result, the focus of attention for understanding the biological roles of quinolinic acid in the CNS became centered on disorders associated with neuronal damage and degeneration (Lee et al., 2016; Lovelace et al., 2016).

By testing other compounds in the kynurenine pathway, a second metabolite, kynurenic acid, was later characterised as a glutamate receptor *antagonist*, blocking the actions of glutamate, NMDA and quinolinic acid, as well as related agonists thought to define other glutamate receptor subtypes, namely quisqualic acid [acting at what are now known as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors] and kainic acid (Perkins and Stone, 1982; Stone and Darlington, 2002). In line with the demonstration that NMDA receptor antagonists prevent excitotoxicity and seizures (Croucher et al., 1982; Schwarcz et al., 1982), kynurenic acid was then soon shown to possess pronounced neuroprotective and anticonvulsant effects (Foster et al., 1984).

Around the same time, interest developed in the biological function of one of the initial enzymes in the kynurenine pathway, indoleamine-2,3-dioxygenase (IDO), which converts tryptophan to kynurenine. Pfefferkorn (Pfefferkorn, 1984) observed that IDO was activated by interferon-ɣ during the immune response to infection, inhibiting the detrimental effects of the infectious agent. This insight triggered a long-running debate on whether the mechanism of the anti-infective effect was caused by the depletion of tryptophan or by the accumulation of kynurenine and its downstream metabolites (Badawy et al., 2016).

Mostly as a result of these early reports, interest in the kynurenine pathway has grown progressively and at an increasing rate, with over 15,000 articles published to date. The kynurenine field now encompasses a wide range of studies in physiology, pharmacology and immunology, with potential clinical relevance in areas as seemingly disparate as neurological and psychiatric diseases, diabetes and cancer (Strasser et al., 2016). In this review, we shall limit ourselves to highlighting a few selected areas of investigation in which there exist important yet largely unresolved questions with regard to basic biology and implications for brain pathology. Subsequent papers in this issue of "Neuropharmacology" address individual topics in more detail to provide a flavour of the growing depth and breadth of interest in the kynurenine pathway.

Kynurenine pathway metabolism: some unsettled basic issues

One important problem facing neurobiologists is that the traditionally accepted scheme of tryptophan metabolism via kynurenine (Figure 1) does not always agree with experimental findings, raising fundamental questions with regard to the origin and disposition of components of the pathway. For example, the concentration of quinolinic acid in the brain does not decline as predicted after pharmacological inhibition or genomic elimination of

kynurenine 3-monooxygenase (KMO). Thus, despite large increases in the brain levels of kynurenic acid (10-100-fold), indicating a shift of pathway metabolism towards the formation of the neuroprotective agent, administration of a selective KMO inhibitor does not affect brain quinolinic acid levels at all (Clark et al., 2005), and even the complete genomic deletion of KMO reduces brain quinolinic acid levels only by around 20% (Giorgini et al., 2013). At the same time, brain levels of anthranilic acid and picolinic acid, two pathway metabolites which have received relatively little attention so far, increase several-fold in these experimental situations.

Two conditions in which these phenomena may be pathophysiologically significant are cerebral malaria and trypanosomiasis. Mice treated with strains of the malaria parasite (*Plasmodium)*, which induce a cellular and cerebral pathology closely resembling that seen in humans, develop progressive cerebral inflammation and behavioural impairments, and die within 7 days (Clark et al., 2005). When treated with the KMO inhibitor Ro 61-8048, however, the animals, which show 100-fold increases in the levels of kynurenic acid and anthranilic acid in the brain, survive for at least 21 days. This raises the possibility that not only kynurenic acid but also anthranilic acid may have beneficial effects in pathological situations that are associated with an inflammatory state. Perhaps it is no coincidence that the molecular structures of many non-steroidal anti-inflammatory and analgesic drugs currently available are built around the anthranilate nucleus (Mohamed Eissa et al., 2012; Sharma et al., 2002).

Many questions remain. If kynurenines are key players in the inflammatory process, are they drivers of functional changes or merely biologically inert bystanders? Are changes in the levels of the metabolites a direct consequence of immune regulations of individual kynurenine pathway enzymes or secondary reactions to entirely different stimuli? What are the differences between acute and chronic inflammation, given that chronic conditions are often associated with compensatory metabolic adjustments?

Another issue of fundamental relevance to neuroscientists pertains to the cellular localization of kynurenine pathway enzymes and their products in the mammalian brain. With exceptions (Guillemin et al., 2007), most studies indicate that brain kynurenines are synthesized or degraded in glial cells rather than in neurons under both normal and pathological conditions. Thus, neuronal lesions, which are typically accompanied by astrogliosis and microglial proliferation, are mostly associated with elevated enzyme activities and higher, rather than lower, levels of pathway metabolites (Ceresoli et al., 1997; Guidetti et al., 1995). The generally accepted view holds that the main branch of the cascade, leading to 3-hydroxykynurenine, 3-hydroxyanthranilic acid, quinolinic acid and beyond, is normally contained in microglial cells whereas kynurenic acid is formed in

astrocytes in a second, competing branch of the pathway (Figure 1). This conclusion is largely based on *in vitro* studies using individual cell types in culture (Chen et al., 2011; Chiarugi et al., 2001; Heyes et al., 1997; Kiss et al., 2003; Kocki et al., 2002) and, unfortunately to a far lesser extent, immunocytochemical analyses with antibodies directed against purified enzymes or against metabolites themselves (Guidetti et al., 2007; Lehrmann et al., 2001). Specifically, in the absence of anti-KMO antibodies that can be used for unambiguous microscopic localization of the enzyme, evidence for a microglial localization of this pivotal pathway enzyme rests mostly on *ex vivo* studies (Guillemin et al., 2005; Parrott and O'Connor, 2015). Notably, however, though the concept of a physical segregation of the two arms of the pathway in the brain is intuitively attractive, the dynamics of cerebral kynurenine pathway metabolism change substantially under abnormal conditions (Hoshi et al., 2009; Parrott and O'Connor, 2015; Saito et al., 1993; Wu et al., 2013). It follows that the cellular localisation of individual pathway enzymes, as well as the functional relationship between the two pathway branches, in the brain ought to be carefully assessed and interpreted in future studies.

A third major challenge for neuroscientists is related to the fact that the influence of peripheral kynurenines on brain function is still not fully understood. Although circulating tryptophan as well as some pathway metabolites (including the pivotal kynurenine and 3-hydroxykynurenine) can enter the brain quite easily under physiological conditions (Fukui et al., 1991; Pardridge, 1998), important open questions abound. For example, since most challenge studies so far have only examined the central effects of *acute* fluctuations in plasma kynurenines, far too little is known about possible qualitative and quantitative adaptations of the blood-brain barrier to *persistent* up- or downregulation of kynurenine pathway metabolism in the periphery. What about the effects of pathological changes in blood-brain barrier permeability, causing abnormalities in endothelial cells and capillary function in specific parts of the brain (Owe-Young et al., 2008)? With regard to possible neuropharmacological applications, can targeted manipulations of the large neutral amino acid transporter, which normally mediates the brain uptake of blood-derived kynurenines (Pardridge, 1983, 1998), be used to influence cerebral pathway metabolism and function?

Molecular sites of action

Over the last decade, a plethora of newly identified molecular sites and receptors have been suggested to mediate the biological effects of the various metabolites of the kynurenine pathway. These novel molecular targets may exist on neurons or various non-neuronal brain cells, or on immune cells in the periphery, presenting significant impediments for the

unambiguous interpretation of data involving pharmacological or genetic manipulations of the pathway.

While quinolinic acid is certainly an agonist at NMDA receptors, various subtypes of NMDA receptors and subunit combinations are differentially sensitive to the metabolite. In particular, quinolinic acid is relatively selective for NMDA receptors in the neocortex and hippocampus, with much weaker activity in the cerebellum and spinal cord (Perkins and Stone, 1983a, b), correlating with the weakness of quinolinate's activity at NR2C subunits (de Carvalho et al., 1996; Monaghan and Beaton, 1991) and the low expression of NR2C and NR2B subunits in the cerebellum (Scherzer et al., 1997; Wang et al., 1995). Quinolinic acid can also generate reactive oxygen species, which may contribute to neuronal damage under pathological conditions (Santamaria et al., 2001).

In addition it is becoming clear that quinolinic acid contributes to many areas of neurobiology and related systems. Many of these topics have been admirably reviewed elsewhere (Guillemin 2012) but include important interactions with the immune system. Pro-inflammatory mediators such as TNFα can promote quinolinic acid production (Guillemin et al. 2001) and interleukin-1β potentiates quinolinate excitotoxicity (Stone and Behan 2007) while suppressors of inflammation such as interleukin-4 inhibit it (Musso et al. 1994). A number of indole-derived compounds as well as structurally related agents can suppress quinolinic acid production by inhibiting TDO (Botting 1995).

Although the direct effects of quinolinic acid are mediated primarily on NMDA receptors, quinolinic acid can also promote the release and inhibit the re-uptake of glutamate (Tavares et al. 2002) potentially facilitating the activation of kainate and AMPA receptors as well as metabotropic glutamate receptors. Furthermore, quinolinic acid has some intracellular actions which are probably independent of membrane receptors involvement. For example, quinolinic acid increases the phosphorylation of several proteins including tau filament proteins implicated in Alzheimer's disease (Rahman et al., 2009; Pierozan et al. 2010).

Kynurenic acid is well established as an antagonist at all ionotropic glutamate receptor subtypes, with greatest potency blocking the obligatory glycine-B co-agonist site on NMDA receptors (Birch et al., 1988a, b). An argument against the physiological relevance of this action is that inhibition is only seen at concentrations that are substantially higher than those normally found endogenously in the CNS. However, upon efflux (whether active or passive) from neurons or glia, concentrations in the immediately surrounding tissue could easily reach levels similar to, or greater than, those known to be pharmacologically active and sufficient to directly affect NMDA receptor-mediated synaptic transmission. By the time kynurenic acid has diffused away from its sites of production, diluted by several orders of magnitude in the extracellular fluid and eventually the cerebrospinal fluid (CSF), its levels will have fallen

substantially. Extracellular concentrations of kynurenic acid will also be reduced by active removal from the brain (Moroni et al., 1988) and cellular re-uptake (Uwai et al., 2012). Together, these factors make it difficult to rely on measurements of *absolute* concentrations of kynurenic acid and other pathway metabolites in tissue, microdialysate, CSF or plasma when attempting to assess target engagement in the context of physiological effects, pathological symptoms, and treatment.

Understanding the mechanism of action of kynurenic acid is especially difficult since the compound appears to have several biological targets in addition to glutamate receptors. One argument against a preferential role of NMDA receptor inhibition is that 7-chlorokynurenic acid, which blocks the glycine-B co-agonist site with approximately 20-fold higher affinity than kynurenic acid itself (Leeson et al., 1991), does not duplicate the actions of kynurenic acid in several experimental paradigms *in vitro* and *in vivo* (Beggiato et al., 2013; Beggiato et al., 2014; Hilmas et al., 2001). On the other hand, 7-chlorokynurenic acid itself may not act as a selective glycine-B antagonist *in vivo* (Lehmann et al., 1993) and even *potentiates* NMDA receptor activation in human embryonic kidney cells (Smothers and Woodward, 2007). Differential affinity of 7-chlorokynurenic acid at glycine binding sites of various NMDA receptor subtypes (Nilsson et al., 2007; O'Shea et al., 1991), possible brain region-specific effects (Linderholm et al., 2007), and the ability of kynurenic acid to modulate extracellular glutamate levels in the brain (see Schwarcz, 2016, for review), further complicate interpretation.

Another potential target is the α7 homomeric nicotinic receptor (Hilmas et al., 2001) though this site, too, has not yet been unequivocally validated. Thus, several independent studies have failed to reproduce the original observations (see Albuquerque and Schwarcz, 2013, for discussion; Arnaiz-Cot et al., 2008; Dobelis et al., 2012; Mok et al., 2009). Other investigators used pharmacological tools such as galantamine, an allosteric enhancer of α7 nicotinic receptor function that acts as an agonist at a site that overlaps with the site targeted by kynurenic acid (Lopes et al., 2007). But the drug also inhibits the activity of cholinesterase and other esterases at higher concentrations (Darvesh et al., 2003; Nordberg and Svensson, 1998), possibly limiting its ability to provide definitive proof for the involvement of α7 receptors in the actions of kynurenic acid. Moreover, galantamine blocks some potassium channels (Vicente et al., 2010; Vigneault et al., 2012), which may be sufficient to explain its facilitatory effect on neuronal transmission and its apparent reversal of the effects of kynurenate.

To add to these complexities, kynurenic acid can also *activate* the G-protein coupled receptor GPR35 (Stone et al., 2013; Wang et al., 2006). Although found primarily on immune cells and in the gastrointestinal tract, this protein does occur in the CNS where it is located

on astrocytes (Moroni et al., 2012) and has been linked to nociceptive phenomena and neurotransmission in the hippocampus (Alkondon et al., 2015). Here, too, the extent to which this activity is relevant physiologically or under pathological conditions remains unclear, requiring further in-depth evaluation. Finally, kynurenic acid is an agonist at the aryl hydrocarbon receptor (AHR) (DiNatale et al., 2010), a xenobiotic-sensing receptor that promotes the metabolism of environmental toxins and functions in immune-regulation (Stephens et al., 2013). This site is present on tumour cells and cells of the immune system, sparking considerable interest in the role of kynurenines in the initiation and development of cancers (Bessede et al., 2014; Opitz et al., 2011). Implications for neurobiology, including neuropharmacology, are not unlikely but have not been explored so far.

One additional aspect that makes the kynurenine pathway increasingly interesting is that kynurenine itself, as well as its metabolites 3-hydroxykynurenine and 3-hydroxyanthranilic acid, are biologically active. Like kynurenic acid, kynurenine is an AHR agonist with unknown downstream effects (Opitz et al., 2011). 3-hydroxykynurenine and 3-hydroxyanthranilic acid are both redox active and may function to regulate and maintain the oxidative status of tissues in order to prevent cell damage by reactive oxygen species (Chobot et al., 2015; Gonzalez-Esquivel et al., 2016; Shibata et al., 2014). In addition, 3-hydroxyanthranilic acid also has distinct actions within the immune system. Target molecules which may function as 3-hydroxyanthranilic acid receptors have been demonstrated on dendritic cells and a range of T cells including Th1 cells and FoxP3+ Treg cells (Xie et al., 2015). While the precise nature of the effects mediated through these sites is still unclear, the overall effect of 3-hydroxyanthranilic acid seems to be anti-inflammatory (Krause et al., 2011). This concept is consistent with studies showing profound changes in 3-hydroxyanthranilic acid concentrations in inflammatory disorders and their normalisation on treatment (Forrest et al., 2006), especially when considered in terms of the ratio with anthranilic acid (Darlington et al., 2010).

Clarification of the differential roles and relevance of these various target sites is clearly a pressing problem and should be pursued with high urgency. Ideally, newly produced selective agonists and antagonists can soon be used as tools to achieve this objective in the laboratory. These experimental agents might then also constitute lead compounds for the development of new drugs which might be suitable in a range of clinical conditions involving kynurenine pathway metabolites.

Technical and methodological considerations

In studies of the role of kynurenines in the CNS, the majority of useful information has been gleaned from work on *in vivo* models or acutely prepared tissue slices, though studies

with freshly dissociated cells (neurons, astrocytes and microglia) have also provided relevant information (Guillemin et al., 2007; Guillemin et al., 2005). In contrast, cell culture systems have proved less valuable and are often controversial. This is a reflection of the fact that cell lines – even those that are purportedly from the same original stock and are labelled as the same cell type – are quite heterogeneous and show progressively changing characteristics with repeated passages (Nugoli et al., 2003). This problem has received most attention in the cancer field, where some of the most widely used cell lines are now known to exhibit substantially different growth patterns and molecular signatures between suppliers and research laboratories (Nugoli et al., 2003; Xie et al., 2012), but often also muddies research of CNS kynurenines. Thus, though observations of intracellular biochemical events or effector targets (receptors, ion channels) of kynurenines in neuronal and glial cultures continue to be useful, great caution must be exercised when extrapolating such data with regard to functional interactions *between* various cell types. The continuous biochemical dialogue between neurons and glia, and between intra- and extracellular compartments of these cells, as well as the presence in the CNS of a considerable number of small molecule regulators of kynurenine pathway metabolism (Chen et al., 2011; Guillemin et al., 2007; Guillemin et al., 2005), present far greater challenges to experimental reproducibility and interpretation than studies using dissociated cells of peripheral origin, such as hepatocytes or myocytes.

   Apart from an increased attention to the role of individual cell populations, it is not difficult to predict that the development of new experimental tools, too, will contribute greatly to solving the many open questions of kynurenine neurobiology. This includes approaches involving the genes of specific pathway enzymes, such as the generation of knockout animals, the search for informative spontaneous mutations and single nucleotide polymorphisms (Aoyama et al., 2006; Holtze et al., 2012; Wonodi et al., 2014), and gene silencing methodologies (Vidal et al., 2015). Moreover, conditional knockouts or knockdown models of each of the kynurenine pathway enzymes are expected to clarify the functional dynamics of pathway metabolism in the CNS in the near future.

   The value of the new information obtained from genetic observations and manipulations will be further enhanced by the use of human or small animal imaging techniques, which can be used to visualize and quantify enzyme expression or activity non-invasively *in vivo*. This will require the design and radioactive labelling of appropriate specific ligands, and may include agonists/activators and antagonists/inhibitors of receptors, enzymes and other proteins that are known to define and determine the functions of kynurenines in the brain. Among many other conceivable applications, successful development of these tools will

make it possible to discriminate between splice variants of proteins or between enzyme isoforms – for example the four subtypes of kynurenine aminotransferase (Han et al., 2010).

The gut-brain axis

As investigators pay increasing attention to the relationship between the gastrointestinal microbiome and the brain, with thousands of bacterial species under constant flux and variation with changes in the diet and nutritional status of the host (Bauer et al., 2016; Ghaisas et al., 2016; Ojeda et al., 2016), it is important to explore the potential role of microbes in the metabolism and function of the kynurenine pathway. Humans and most other mammals do not have the ability to synthesise tryptophan, which is therefore considered an "essential" amino acid. In contrast, tryptophan is readily neosynthesised by most plants and bacteria (Barends et al., 2008; Marinoni et al., 2008; Turski et al., 2011).

Interestingly, bacteria also utilize other mechanisms which account for the formation and degradation, respectively, of neuroactive kynurenines. For example, bacteria can neo-synthesize quinolinic acid (Marinoni et al., 2008; Reichmann et al., 2015; Sakuraba et al., 2005; Saunders et al., 2008), and unique prokaryotic enzymes can degrade kynurenic acid (Taniuchi and Hayaishi, 1963). Bacterial neosynthesis of quinolinic acid begins with the condensation of iminoaspartate with dihydroxyacetone, and the latter compound also inhibits α-amino-β-carboxymuconate-ε-semialdehyde decarboxylase (ACMSD) (Garavaglia et al., 2009). Normally, ACMS cyclises non-enzymatically to quinolinic acid, but is converted to picolinic acid in the presence of ACMSD. Inhibition of ACMSD by bacterial dihydroxyacetone will therefore increase the synthesis of quinolinic acid. Another source of quinolinic acid may be anthranilic acid (first converted to 3-hydroxyanthranilic acid by anthranilate oxidase; Liu et al., 2010), and bacteria can also produce quinolinic acid non-enzymatically (Cleaves and Miller, 2001). These bacterial processes may play a part in – still ill-defined – biological roles of endogenous quinolinic acid in the mammalian brain. We predict that more detailed information on these alternative processes involving the gut microbiome will be essential to understand fully the dynamics of cerebral tryptophan metabolism and, in particular, the balance between quinolinic acid and kynurenic acid production and function in the brain. In other words, it is tempting to speculate that microbially-regulated tryptophan and kynurenines significantly influence CNS function and dysfunction in mammals (Kennedy et al., 2016; O'Mahony et al., 2015).

CNS development

The nature and possible functional role of kynurenines in the developing brain has begun to receive increased attention in recent years. In rodents, the fetal brain contains remarkably

high concentrations of neuroactive kynurenines compared to the adult brain (Ceresoli-Borroni and Schwarcz, 2000), and a similar observation has been made with regard to prenatal cerebral kynurenic acid levels in non-human primates (Beal et al., 1992). As the brain content of all these metabolites falls off precipitously immediately after birth, the high fetal brain levels likely originate either from the maternal circulation or from the placenta. Still, various scenarios may account for the high prenatal levels of brain kynurenines. Possibilities include, for example, relatively unimpeded transport of kynurenine and/or 3-hydroxykynurenine from the maternal blood or the placenta to the fetal brain and, subsequently, robust production of downstream metabolites due to high activities of kynurenine pathway enzymes in the fetal brain. Alternatively or in addition, and in contrast to their very low ability to penetrate the blood-brain barrier in adulthood (Fukui et al., 1991), the polar compounds kynurenic acid and quinolinic acid, derived from the mother or the placenta, may be able to enter the fetal brain relatively freely. These fundamental principles of kynurenine neurobiology are readily testable experimentally. Detailed knowledge is overdue and will significantly impact our thinking about the possible physiological role of the high brain levels of kynurenines during the prenatal period.

The term 'neuro-developmental diseases' has been coined to refer to disorders that appear in late childhood or adulthood but are caused by abnormal early development of the CNS. In principle, early developmental impairments may be genetic in origin or caused by adverse external influences including bacterial or viral infections, exposure to environmental or dietary toxins, or experience of stressful situations (O'Farrell and Harkin, 2016). It is now recognised that these factors directly affect the kynurenine pathway in at least three general ways. Firstly, infections induce an immune response which raises the production of several cytokines such as interferon-γ, interleukin-1β and tumour necrosis factor-α (TNF-α). These as well as other pro-inflammatory cytokines in turn induce tryptophan 2,3-dioxygenase (TDO) and KMO and therefore increase pathway flux (Pemberton et al. 1997; Smith et al., 2001)

Secondly, psychological stress causes increased synthesis and secretion of adrenal glucocorticoid hormones, which in turn affect kynurenines both in the periphery and in the brain (Laugeray et al., 2010). Thirdly, some naturally occurring compounds such as the brassinins, found in a number of vegetables, can inhibit IDO and thus reduce activity along the entire kynurenine pathway (Banerjee et al., 2008; Gaspari et al., 2006).

The fundamental importance of these links between kynurenine pathway metabolism and brain development is particularly apparent when considering the influence of environmental factors on the embryonic brain. Infection by viruses, bacteria or parasites is associated with the activation of Toll-Like Receptors (TLRs), especially TLR3 and TLR4, which can be

activated experimentally by agents such as bacterial lipopolysaccharide (LPS) or the viral-mimetic double-stranded RNA poly(inosinic:cytidylic) acid (poly I:C). TLR activation results in stimulation of the kynurenine pathway (Asp et al., 2010; Clarke et al., 2012; Opitz et al., 2009; Suh et al., 2007; Wang et al., 2011), so that any infection contracted during pregnancy is likely to be accompanied by increased production of kynurenines. This effect may depend on the age at which TLR activation occurs (Khalil et al., 2013). In light of the fact that changes in kynurenine metabolism affect brain development (Forrest et al., 2013a; Forrest et al., 2013b), with consequences which persist into adulthood (Forrest et al., 2013b; Notarangelo and Pocivavsek, 2016; Pisar et al., 2014), any infection during the very early stages of brain development may therefore result in CNS dysfunction, or increased susceptibility to dysfunction, later in life. For example, in rats, perinatal administration of influenza virus stimulates cerebral kynurenine pathway metabolism acutely, resulting in impaired sensorimotor function in adulthood (Asp et al., 2010). As human brain development continues for several years after birth (Ballesteros et al., 1993; Gogtay et al., 2004; Jernigan et al., 2011), spanning times when children are exposed to a range of harmful environmental influences, these studies suggest that the vulnerable period may, in fact, extend into the early years of childhood in humans. Activation of the kynurenine pathway could certainly explain the emergence of psychiatric disorders in people born to mothers exposed to a range of infectious organisms including Toxoplasma gondii,rubella, influenza and cytomegalovirus (Hunt et al., 2016; Libbey et al., 2005; Torrey et al., 2007; Torrey et al., 2012; Yolken and Torrey, 2008) or to persistent stressful events *in utero* and beyond.

In view of the central role of glutamatergic mechanisms in brain development (Metzger, 2010), impaired glutamate function in the brain could constitute a common molecular mechanism linking perinatal imbalance of kynurenines to subsequent vulnerability and pathology. Indeed, prenatal interventions affecting kynurenine pathway metabolism affect the expression of glutamate receptor subunits (Forrest et al., 2013a; Forrest et al., 2013b), and abnormalities of glutamate-related cognitive performance are seen after repeated early stress (Tse et al., 2011; Yuen et al., 2012). It is therefore not difficult to predict that the nature and effects of imbalanced glutamatergic neurotransmission following abnormal kynurenine pathway metabolism during brain development will become a major focus of investigation for many years to come.

Finally, although not directly related to CNS function, it is important to note the crucial role played by IDO and its regulation at the earliest stages of implantation, embryogenesis, maternal immune tolerance and the maternal-fetal balance. These factors and interactions, (reviewed by Badawy et al. 2016; see Stone 2016) are important influences on the initiation

and maintenance of a successful pregnancy and hence a complete and normal CNS development.

CNS diseases: Huntington's disease as an example

As described and discussed in several articles in this issue of "Neuropharmacology", dysfunctions in kynurenine pathway metabolism have been tentatively linked to the etiology of a considerable number of CNS diseases. Paradigmatically, we are limiting our comments here to the potential role of kynurenines in the pathogenesis of the neurodegenerative disorder HD, which is inherited in an autosomal dominant fashion. As noted earlier, this hypothesis originated more than three decades ago with the demonstration that an intrastriatal injection of quinolinic acid in rats duplicates an array of neuropathological, neurochemical and behavioural features that are characteristic of the human disease (Schwarcz et al., 2010). Subsequent post-mortem studies in humans revealed a significantly increased activity of 3-hydroxyanthranilic acid dioxygenase, the immediate biosynthetic enzyme of quinolinic acid, in brain tissue of HD victims compared to controls (Schwarcz et al., 1988), and found substantially elevated levels of quinolinic acid in cortex and striatum of patients who had died in the early stages of the disease (Guidetti et al., 2004). In apparent further support of a pathophysiologically significant connection to kynurenines, the same HD samples also showed greatly increased levels of 3-hydroxykynurenine, which generates highly reactive free radicals and thereby potentiates the neurotoxic effects of quinolinic acid (Guidetti and Schwarcz, 1999).

The fact that HD is well understood from a genetic perspective offers new opportunities for assessing the role of the kynurenine pathway in pathology. The protein huntingtin, which holds the key to the disorder, is located on the short arm of chromosome 4 and contains a terminal poly-glutamine repeat chain, which is normally up to about 35 residues in length. If the chain length exceeds 40 residues, individuals exhibit HD symptoms. The severity of symptoms and disease progression increase with increasing numbers of glutamine repeats on mutant huntingtin (Forrest et al., 2010). This linkage allows investigators to directly test the involvement of molecular entities such as kynurenines in the disease process, and supportive data have been obtained in several genetic HD mouse models (Schwarcz et al., 2010). In a study in humans, HD patients and their healthy relatives ($\leq$ 35 glutamine repeats) were classified into four groups based on symptom severity – no, few, moderate or severe. Samples of saliva were then collected for the determination of the number of poly-glutamine repeats, and blood was taken for the analysis of tryptophan and kynurenine in the serum. The results revealed highly significant correlations between the kynurenine/tryptophan ratio, i.e. the activity of the initial oxidative step in the kynurenine pathway, and both symptom

severity and – crucially – the length of the poly-glutamine expansion in mutant huntingtin (Forrest et al., 2010). These results naturally raise a host of interesting questions and are especially intriguing on principal grounds, supporting the hypothesis that a genetically determined increase in kynurenine pathway activity may indeed contribute to the symptoms and disease progression in HD. More generally, this comprehensive approach, combining genetic assays and systematic clinical evaluations with chemical analyses in blood or other readily accessible body fluids, represents a promising model for the study of other CNS disorders with suspected etiological connections to kynurenines.

Future directions

As demonstrated above using selected examples, studies of kynurenine neurobiology have begun to diversify into many areas of interest. Additional recent discoveries illustrate the unpredictability of the field and at the same time highlight entirely new, translationally relevant research trajectories. Thus, work by Ruas and collaborators recently revealed that the skeletal muscle enzyme PGC1α1 modulates kynurenine metabolism and at the same time causes resilience to depression caused by chronic mild stress (Agudelo et al., 2014). Specifically, the authors report that the enzyme, when induced by exercise, up-regulates kynurenine aminotransferase activity and reduces circulating kynurenine levels, and propose that this effect is critical for the well-established antidepressant consequences of exercise in animals and humans. Although the study does not clarify the mechanism(s) by which *brain* kynurenines might be involved, this intriguing study implies that the treatment of depression might be possible by pharmacological modulation of PGC activity – in effect postulating an "exercise pill" based on modulating kynurenine pathway metabolism.

Another recent study, describing the effects of nutritional restriction on tryptophan degradation along the kynurenine pathway, may also be relevant for the pathophysiology of depression since altered appetite is a common symptom of the disease. Thus, in the nematode *C. elegans*, reduced intake of tryptophan was found to lower the levels of kynurenic acid, allowing increased activation of NMDA receptors. This, in turn, resulted in higher activity of neuropeptide Y-containing cells, which secondarily promoted feeding behaviour by stimulating serotonergic neurons (Lemieux et al., 2015). This intriguing neurochemical cascade is consistent with studies in mammals, which show that feeding is promoted by the activation of serotonin 2C receptors (Voigt and Fink, 2015). Indeed over-activation of these receptors may contribute to abnormally high appetite and, ultimately, obesity. In line with these findings and observations, it will be interesting to explore whether modification of kynurenine pathway metabolism, and specifically a reduction of kynurenic acid synthesis, holds promise as an intervention to achieve appetite reduction in humans.

Another noteworthy study in *C. elegans* demonstrated that a loss of TDO2 activity reduces neuronal death associated with three potent neurotoxic peptides: α-synuclein, amyloid-β and extended poly-glutamine peptides (van der Goot and Nollen, 2013; van der Goot et al., 2012). These findings imply that TDO2 may normally facilitate the toxicity of the peptides, possibly involving a distinct site on the TDO2 molecule which normally regulates protein metabolism. Intriguingly, a reduction in TDO2 expression also results in a prolongation of lifespan in the worms (see Badawy, 2016; Oxenkrug et al., 2011). If these remarkable effects can be duplicated in mammals, efforts to decipher the underlying molecular mechanism(s) will certainly multiply. One of the many questions to be addressed is whether similarly impressive effects can be achieved by down-regulation of IDO and TDO1, which are highly conserved orthologs of TDO2.

Another topic that deserves careful study and is beginning to receive increasing attention is the link between kynurenines and stem cell biology. Human and mouse mesenchymal and neural stem cells express the entire kynurenine pathway (Croitoru-Lamoury et al., 2011), and pluripotent adult progenitor cells have IDO-dependent immunomodulatory properties, implicating kynurenine, and possibly its downstream metabolites, as effectors (Jacobs et al., 2013). Of the many open questions, clarification of the mechanisms by which kynurenines influence stem cell proliferation and differentiation may be of greatest interest to cell biologists and other pre-clinical researchers. However, a thorough understanding of these effects will also increase the likelihood of success of stem cell-based therapies in a variety of infectious and inflammatory diseases affecting the brain.

In the context of depressive illness, there is a pressing need to clarify whether kynurenines are *unequivocally* involved in pathophysiology. The existence of this connection, specifically a role of an immune-stimulated increase in cerebral quinolinic acid levels in pathogenesis, has been repeatedly proposed, but the hypothesis has not been fully confirmed so far (Clark et al., 2016). Notably, changes in kynurenine pathway metabolism may be preferentially, or even exclusively, seen in patients with suicidal intent (Bradley et al., 2015; Bryleva and Brundin, 2016; Sublette et al., 2011). Here, the levels of kynurenic acid were significantly reduced in patients and correlated with the severity of depressive symptoms. Conceivably, therefore, the disease may be causally related to an imbalance between quinolinic acid and kynurenic acid in the brain, with a relative abundance of the former leading to enhanced NMDA receptor function and symptoms of depression. It is interesting to speculate that the primary biochemical defect in depressive states may lie in the generation of kynurenic acid, leaving increased levels of kynurenine to be converted to quinolinic acid, whereas in schizophrenia the primary cause is more likely to be dysfunction of KMO (Holtze et al. 2012; Wonodi et al. 2011, 2014) which interrupts the formation of

quinolinic acid and diverts kynurenine towards kynurenic acid. Of note, this scenario would not only explain the efficacy of NMDA antagonists as rapidly acting antidepressants (Coyle and Laws, 2015; Drewniany et al., 2015; Machado-Vieira et al., 2009) but raises the possibility that interventions causing an elevation of brain kynurenic acid levels may provide clinical benefits in the disease.

New genetic information, too, will provide valuable insights into the roles of kynurenines in physiological processes and, in particular, in pathological phenomena affecting the CNS. The presence and remarkable conservation of most elements of the kynurenine pathway in organisms ranging from prokaryotes to humans, together with the recent development of highly sophisticated and precise molecular tools to study and manipulate DNA or RNA, will undoubtedly generate novel – and testable – biological hypotheses. One of the most interesting experimental targets in this regard is the pivotal pathway enzyme KMO. In fact, specific genetic features such as distinct single nucleotide polymorphisms in *Kmo* in patients with schizophrenia (see above), and reduced levels of the mRNA for KMO in prefrontal cortex tissue from patients with bipolar disorder with psychotic features (Lavebratt et al., 2014), have been identified in recent years. Interestingly, the latter study revealed, specifically, an association between a KMO Arg(452) allele and manic psychosis, and between this allele and raised levels of kynurenic acid in these patients. All these findings await verification in larger cohorts and, subsequently, careful evaluation of functional consequences.

Finally, we assert that thorough investigations of the relationship between kynurenines and other (neuro)biologically active tryptophan metabolites are overdue and of fundamental importance. Although functionally significant interactions between kynurenine pathway metabolites and other prominent tryptophan products such as serotonin and melatonin are not unlikely, far too little is known in this respect. In the brain as in the periphery, cross-talk of the various catabolic branches of tryptophan, perhaps also involving additional metabolites such as tryptamine, will surely turn out to be complex, and elucidation will be challenging. Uni- or bi-directional influences could well vary with brain region, life stage, circadian rhythm and physiological requirements, and may differ among species. Most likely, pathological events will need to be assessed individually in this respect, though commonalities may exist in maladies with shared features, for example excitotoxic neurodegeneration or abnormalities of the immune system.

Summary and final comments

Research on the neurobiology of the kynurenine pathway has suffered years of relative obscurity because tryptophan degradation, and its involvement in both physiology and major

brain diseases such as depression, schizophrenia (Erhardt et al., 2016) and neurodegenerative disorders, was viewed almost exclusively through the lens of the well-established metabolite serotonin (and to some extent melatonin). With increasing recognition that kynurenine and its metabolites can affect and even control a variety of classic neurotransmitter systems directly and indirectly, interest is expanding rapidly. Moreover, as evidence accumulates that, in turn, kynurenine pathway metabolism itself is modulated in conditions such as infection and stress, which are known to induce major changes in well-being and behaviour, it is also becoming apparent that kynurenines may be instrumental in the *etiology* of psychiatric and neurological disorders (Fujigaki et al., 2016; Hunt et al., 2016). It is therefore likely that the near future will not only witness the discovery of additional physiological and pathological roles for brain kynurenines, but also ever-increasing interest in drug development based on these roles. In particular, targeting the kynurenine pathway with new specific agents may make it possible to *prevent* disease by appropriate pharmacological manipulations (Dounay et al., 2012; Dounay et al., 2015; Jayawickrama et al., 2015; Stone and Darlington, 2013; Wu et al., 2014; Zwilling et al., 2011). Knowledge of the kynurenine pathway will be central to one of the cardinal achievements of medical research – averting disease rather than treating its symptoms.

We focused here on areas of kynurenine research which are either controversial, of major potential therapeutic interest, or just beginning to receive the degree of attention which will clarify their relevance to neurobiology and medicine. We also highlighted technical issues which require careful consideration in study design, experimental approaches and data evaluation. Although several of these concerns are not unique to the kynurenine pathway, we feel that it is important that investigators entering the field, and new research initiatives, are not misdirected by misleading results or incorrect interpretations at this time of skyrocketing interest in the subject matter.

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Figure legend

Figure 1: The kynurenine pathway of tryptophan degradation