The kynurenine pathway as a therapeutic target in cognitive and neurodegenerative disorders

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Abstract

Understanding the neurochemical basis for cognitive function is one of the major goals of neuroscience, with a potential impact on the diagnosis, prevention and treatment of a range of psychiatric and neurological disorders. In this review, the focus will be on a biochemical pathway that remains under-recognised in its implications for brain function, even though it can be responsible for moderating the activity of two neurotransmitters fundamentally involved in cognition – glutamate and acetylcholine. Since this pathway – the kynurenine pathway of tryptophan metabolism - is induced by immunological activation and stress it also stands in an unique position to mediate the effects of environmental factors on cognition and behaviour. Targetting the pathway for new drug development could, therefore, be of value not only for the treatment of existing psychiatric conditions, but also for preventing the development of cognitive disorders in response to environmental pressures.

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The neurochemistry of cognition

The neural complexity of cognitive function makes it exceptionally difficult to identify specific neurochemical substrates, especially those that could provide pharmacologically relevant targets for the prevention or treatment of cognitive dysfunction (Millan et al., 2012). The two systems which have received most attention to date are those releasing glutamate or acetylcholine as their transmitters. Both these systems have well-established roles in various aspects of cognitive function, with the focus of interest being on glutamate receptors sensitive to the synthetic ligand N-methyl-D-aspartate (NMDA) (Newcomer & Krystal, 2001; Castellano et al., 2001; Neill et al., 2010).

The biomedical relevance of these systems is borne out by the ability of agonists and antagonists to affect cognitive behaviour and for some of these compounds to appear as potential therapeutic agents. Compounds that promote activation of NMDA receptors, especially

those such as D-cycloserine which act via the co-agonist strychnine-insensitive Gly-B-site for glycine on the NMDA receptor, facilitate learning in humans (Kalisch et al., 2009; Onur et al., 2010) whereas antagonists such as ketamine, dizocilpine [MK-801] and phencyclidine are detrimental to learning and cognitive function (Jentsch & Roth, 1999; Newcomer et al., 1999; Cochran et al., 2003). Major advances are being made in this area relating receptor subunit composition to behavioural relevance. For example, mice that overexpress GluN2B subunits show increased cognition and enhanced plasticity (Cui et al., 2011). While this level of detailed, molecular knowledge about receptors should lead to improved selectivity of drug treatments, it is equally important to understand the mechanisms leading to the activation or modulation of those receptors, including those involving the kynurenine pathway.

The tryptophan-kynurenine pathway

Decades of interest in the metabolic products of tryptophan have focussed on 5-hydroxytryptamine (5-HT or serotonin). However, the synthesis of 5-HT is now known to account for the metabolism of only 3% or less of non-protein tryptophan. The kynurenine pathway, in contrast, accounts for approximately 90% of tryptophan metabolism in most tissues (Stone & Darlington 2002).

The kynurenine pathway (Fig. 1) was identified in the early years of the twentieth century as the catabolic source of one of the newly recognised vitamins - vitamin B3 (nicotinic acid, nicotinamide or niacin). It was regarded solely as a route for the endogenous production of the vitamin to compensate for any dietary deficiency. The first product of tryptophan oxidation by the haemoprotein enzymes indoleamine-2,3-dioxygenase (IDO, found in most tissues) and tryptophan-2,3-dioxygenase (TDO, found mainly in the liver) is kynurenine, a compound identified originally in studies of the chemical composition of canine urine, from which it takes its name. The breakthrough into cognitive neuroscience came when two of the major components of the pathway – quinolinic acid and kynurenic acid - were shown to act on NMDA receptors (NMDAR).

Quinolinic acid

Quinolinic acid was originally found to excite neurones in the cerebral cortex of anaesthetised rats, an effect that was prevented by selective antagonists at NMDAR (Stone & Perkins, 1981). These receptors remain the most important sites of action of quinolinic acid, largely accounting for both its excitatory activity and its ability to produce axon-sparing excitotoxicity (Schwarcz et al., 1983).

There may be additional sites of action of quinolinic acid, although these have not yet been explored in detail. Thus it can generate, or promote the formation of, reactive oxygen species and has a generally pro-inflammatory profile within the immune system, increasing the expression and secretion of chemotactic molecules such as monocyte chemoattractant protein-1 (MCP-1) and Regulated on Activation, Normal T cell Expressed and Secreted (RANTES) (Guillemin et al., 2003). These compounds can originate from several types of immune-competent cells peripherally but are also released by microglia in the central nervous system (CNS). Both proteins attract immune-activated macrophages, which secrete inflammatory cytokines including tumour necrosis factor-α (TNFα). In addition to modulating neuronal excitability, therefore, quinolinic acid can also act as an initiator and promoter of local inflammation within the CNS.

Kynurenic acid

Kynurenic acid is a product of tryptophan metabolism produced by the transamination of kynurenine by kynurenine aminotransferases (KAT) (Fig. 1). Kynurenic acid is an antagonist at glutamate ionotropic receptors responding to amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate or NMDA (Perkins & Stone 1982), although it is most active at the latter. The antagonism of NMDA results from kynurenic acid's binding largely at the Gly-B site on the NMDAR complex (Stone & Darlington 2002). Additional sites of action for kynurenic acid have

been reported recently such as the aryl hydrocarbon receptor (AHR) and the G-protein coupled receptor GPR35 (Stone et al., 2013) but their significance for brain function remains unclear.

Kynurenines and cognitive function

A direct examination of the effects of kynurenines on brain neurochemistry and behaviour in experimental animals and their roles in cognitive disorders in human patients has supported the view that this pathway plays a key role not only in several aspects of cognitive function but also in mediating the effects of environmental influences on cognition.

The simplest of the kynurenine metabolites to manipulate experimentally is kynurenic acid since its concentrations in the brain can be increased substantially by the simple expedient of administering its precursor, kynurenine, which readily crosses the blood-brain barrier. Kynurenate levels can also be raised by inhibiting the enzyme kynurenine-3-monoxygenase (KMO; also known as kynurenine-3-hydroxylase; Fig. 1) (Röver et al., 1997), which normally oxidises kynurenine to 3-hydroxykynurenine (3HK). Inhibition of KMO, therefore, increases the amount of kynurenine available for transamination to kynurenic acid.

Increasing cerebral kynurenate levels in this way produces behavioural and cognitive changes similar to those encountered in psychiatric conditions. Prominent among these changes are effects on sensory processing exemplified by changes in pre-pulse inhibition of auditory startle stimuli (Nilsson et al., 2006). This phenomenon has received a great deal of attention since, although it occurs in a number of psychiatric conditions, it is particularly prominent in schizophrenia and is reduced by treatment with antipsychotic drugs. It is usually considered to reflect sensorimotor gating and integration, properties that may underlie some of the confusional state that exists in early phases of schizophrenia. The ease with which endogenous levels of kynurenic acid can be increased to alter pre-pulse inhibition (Erhardt et al., 2004; Nilsson et al., 2006) favours the concept that a pathological change in the kynurenine pathway could be involved in psychiatric dysfunction

Increased levels of kynurenic acid have also been linked with deficits of spatial working memory (Chess et al., 2007). A particularly fascinating aspect of this finding is that it occurs not only after the acute elevation of kynurenate in adult animals, but also in adults several months after raising kynurenate levels peri-natally or during adolescence (Akagbosu et al., 2012; Pocivavsek et al., 2012). This latter observation presents an intriguing parallel with current views on the development of schizophrenia which suggest a neurodevelopmental origin established pre- or neo-natally and leading to the emergence of behavioural disorder in later life. In addition to spatial learning, kynurenic acid levels modulate stimulus processing and conditioned responding, while later work discovered changes in contextual fear conditioning and context discrimination (Chess et al., 2006). There is some selectivity in these actions, however, since cue-specific fear conditioning is not affected (Chess et al., 2009).

More recently, attention has moved to more sophisticated tests of cognitive performance. Increasing kynurenic acid levels by injections of kynurenine has been found to produce deficiencies in attentional set-shifting paradigms. While the treated and control animals tested were all able to acquire the initial, simple, compound discrimination and the moderately difficult intra-dimensional shift, animals with elevated CNS kynurenate exhibited deficits in acquiring and handling the extra-dimensional shift task (Alexander et al., 2012; Pocivavsek et al., 2012)

Although the artificial elevation of kynurenate levels is a valuable experimental approach to modelling a possible pathological state, it does not address the question of whether normal, physiological levels of kynurenate are involved in baseline cognitive function. This question has been addressed by lowering the levels of endogenous kynurenate. The deletion of the major KAT isoenzyme KAT-II results in a substantial (approximately 70%) decrease in the extracellular concentration of kynurenic acid in the rat CNS and this is accompanied by improved cognitive performance in a range of behavioural tasks including exploration, object recognition, and passive avoidance learning (Potter et al., 2010). These effects are paralleled by alterations of neuronal excitability and plasticity demonstrated by electrophysiological recordings in the hippocampus. Importantly, the selectivity of the kynurenic acid change resulting from KAT-II

deletion was confirmed by the fact that there were no associated changes in the levels of the NMDAR agonist quinolinic acid (Sapko et al., 2006). It is work of this kind that has led to the development of KAT inhibitor compounds for potential use as cognitive enhancers (Rossi et al., 2010; Dounay et al., 2012).

Cognitive disorders

Schizophrenia

One of the disorders characterised almost exclusively by cognitive dysfunction is schizophrenia. A widely accepted current view of this disorder is that it results from under-activation of glutamate receptors – the 'hypo-glutamatergic' hypothesis. This concept has expanded the earlier focus on dopamine function in which the fundamental problem was thought to be overactivity of dopaminergic neurons in the ventral tegmento-striatal (accumbens) projections, associated with metabolic hypo-function in the prefrontal cortex (PFC). It now seems likely that changes in glutamate neurotransmission represent the more biochemically proximal defect in schizophrenia, which can lead secondarily to altered dopamine release and/or receptor expression. Certainly a primary role for glutamate is supported by the development of animal models showing cognitive deficits related to those in schizophrenia but induced by sub-chronic treatments with NMDAR antagonists such as ketamine, dizocilpine [MK-801] or phencyclidine (Jentsch & Roth, 1999; Newcomer et al., 1999; Cochran et al., 2003). The use of phencyclidine in particular reproduces cognitive abnormalities seen either in the early positive or later negative phases of schizophrenia, including dysfunctional sensorimotor and contextual integration or pre-pulse inhibition (Jentsch & Roth, 1999; Phillips & Silversteinr, 2003; Cochran et al., 2003). These deficits are difficult to reproduce with older, dopamine-centred models (Lindsley et al., 2006).

The concentration of kynurenic acid is increased within brain tissue or cerebrospinal fluid (CSF) of patients with schizophrenia, a result that has been replicated by several groups in different cohorts of patients (Schwarcz et a l., 2001; Erhardt et al., 2004; Nilsson et al., 2005,

2006).The concentrations of kynurenic acid were several-fold higher than in normal control subjects, especially in the prefrontal cortex (PFC) where, as noted above, the ‘hypo-frontality’ characterised by reduced metabolic function has become the focus of interest in studies of schizophrenia. As predicted on this hypothesis, treatment with neuroleptic drugs reduces kynurenic acid levels in rodents (Ceresoli-Borroni et al., 2006).

The reason for the elevation of kynurenic acid concentrations in schizophrenia is still unclear although it may be caused by reduced levels of the enzymes KMO and 3-hydroxy-anthranilic acid oxidase (3HAO) (Fig. 1). The mRNA, protein levels and activity of these enzymes are reduced in post-mortem samples of PFC from schizophrenic patients, while activities of the first enzyme of the pathway (IDO), KAT and quinolinate phosphoribosyl transferase (QPRT) are normal (Sathyasaikumar et al., 2011; Wonodi et al., 2011). Experimentally, administration to rodents of the KMO blocking compound 3,4-dimethoxy-N-[4-(3-nitrophenyl)thiazol-2-yl]benzenesulphonamide (Ro61-8048; Röver et al., 1997) produces a clear increase in kynurenic acid concentrations, supporting the concept that reducing enzyme activity does increase kynurenine production (Cozzi et al., 1999; Clark et al., 2005).

Although there are few studies to date on the genetics of tryptophan catabolism in relation to schizophrenia, there is an association between a single nucleotide polymorphism of KMO (rs1053230) and levels of kynurenic acid in the CSF (Holtze et al., 2012). The amino acid change produced by this mutation was considered important for the interaction between enzyme and its substrate (kynurenine) and may be considered a proof-of-concept that a minor genetic alteration can lead to increased kynurenic acid production.

While most of these studies have been performed on CNS tissue or CSF, there are reports of lowered kynurenic acid concentrations in the blood of patients (Myint et al., 2011) or a social isolation-induced rodent model (Moeller et al., 2012). The uncertain relationship between brain and blood measurements places serious limitations on the value of the latter for interpretation of events with the CNS, but a resolution of the discrepant results might lie in the role of the immune system in schizophrenia. The literature on individual cytokine levels or gene

polymorphisms in schizophrenia is confusing and often contradictory, but there seems to be a consensus that immune activation contributes to the symptomatology of the disorder, especially in acute exacerbations of the disease. Increased immune function, primarily in the blood, tends to induce the tissue expression and activity of both IDO and KMO, leading to higher levels of most kynurenine metabolites. Increased levels of kynurenine will pass into the brain and generate increased kynurenic acid which, as a charged, acidic molecule, will be trapped within the brain. This may be further enhanced by the presence of increased concentrations in the PFC of tumour necrosis factor-α (TNF-α) (Paterson et al., 2006) and other pro-inflammatory compounds which activate IDO. The conversion of kynurenine to kynurenic acid will induce the diffusion and transport of more kynurenine from the periphery. The various apparently conflicting data may therefore be integrated in a model that takes these peripheral and central pharmacokinetic factors into account to explain raised kynurenine and kynurenic acid levels in the CNS, at the same time as reduced levels in blood.

At the neurochemical level, increasing kynurenate levels in experimental animals *in vivo* increases the activity of dopaminergic neurons (Nilsson et al., 2006; Linderholm et al., 2007) and facilitates the dopamine release induced by amphetamine (Olsson et al., 2012). On the other hand, several studies which have examined directly the release and extracellular concentrations of dopamine have shown that kynurenic acid decreases dopamine levels in the striatum (Rassoulpour et al., 2005). These results are supported by the inhibition or deletion of KAT, which leads to reduced concentrations of kynurenate and which increases dopamine release in the striatum (Amori et al., 2009). Some of these changes in dopamine release may be indirectly caused by effects of kynurenate on glutamate levels which are decreased in the striatum, hippocampus or PFC by local applications of kynurenate or treatment with kynurenine (Carpenedo et al., 2001; Pocivavsek et al., 2011, 2012). Indeed, kynurenate appears to be a physiological modulator of glutamate and dopamine release, since release of both is increased when resting, endogenous levels of kynurenate are reduced by deleting KAT (Potter et al., 2010; Pocivavsek et al., 2011). The reduction in extracellular glutamate levels by kynurenic

acid is accompanied by impaired performance of mice or rats in tests of cognitive function such as the water-maze test for visuospatial memory and passive avoidance paradigms, while inhibition of KAT and the resulting lowering of kynurenic acid levels produces increased glutamate release and improved performance in these tasks as well as object exploration, object recognition, and spatial discrimination. These facilitated behaviours were associated with increased synaptic plasticity at the cellular level, reflected in greater long-term potentiation in the hippocampus *in vitro* (Pocivavsek et al., 2011).

Some of the data discussed here may be relevant to other conditions in which psychosis forms a major symptom. Thus, a proportion of patients infected with the human immunodeficiency virus (HIV) may develop severe psychotic symptoms resembling those seen in schizophrenia. In these patients the symptom severity appears to relate to the levels of kynurenic acid in the CSF (Atlas et al., 2007; Kandanearatchi & Brew, 2012).

Dementia

Dementia appears in various guises such as Alzheimer's disease and vascular dementia or, as it is now believed, combinations of these two conditions. Early studies focussed on the potential neurotoxic effects of quinolinic acid, based on the several hundred-fold increase in the levels of this compound in the CSF of patients with HIV-linked dementia (Heyes et al., 1991). This disorder, now often known as HIV-Associated Neurocognitive Disorder (HAND) (Kandanearatchi & Brew, 2012) is usually reversible as the infection is treated and quinolinic acid concentrations fall.

Symptoms are accompanied by invasion of the CNS by inflammatory cytokines which gain entry after internalisation by peripheral monocytes and macrophages which enter the CNS before being transformed into microglia. Growing evidence suggests the existence of an inflammatory component in dementia in which quinolinic acid may be involved by means of its ability to induce the expression of chemokines such as MCP-1 and RANTES as noted above (Guillemin et al., 2003). These pro-inflammatory molecules are produced by immune-competent

cells in the periphery and by microglia in the CNS – cells functionally related to, and developed from, macrophages. A major action of MCP-1 is to attract and activate macrophages which release more quinolinic acid and potent inflammatory cytokines including the powerfully pro-inflammatory TNFα. Quinolinic acid can, therefore, initiate and promote the development of local inflammation within the CNS, a situation thought to lead to brain damage subsequently.

It has not proved possible to show any simple relationship between quinolinic acid and dementia in other conditions such as Alzheimer's disease, even though deposits of β-amyloid proteins in the brain are characteristic of Alzheimer's disease and links have been noted with activity along the kynurenine pathway. Activity of IDO and quinolinic acid concentrations are increased in the amyloid plaques and microfibrillary tangles (Bonda et al., 2010; Guillemin et al., 2005) and β-amyloid peptides can induce IDO and kynureninase activities (Guillemin et al., 2003; Walker et al., 2006). Quinolinic acid produces glial activation and cytokine release consistent with a role in the inflammatory and cytotoxic processes occurring in Alzheimer's disease (Ting et al., 2009) while pro-inflammatory cytokines potentiate the activation of IDO by β-amyloid fragments including the most toxic Aβ(1-42) (Yamada et al., 2009), establishing a damaging positive feedback cycle. Nevertheless, there may be a more direct relationship between dementia and kynurenic acid, since levels of this compound in the blood and brain, together with the activity of IDO, increase with age to the extent that they correlate well with cognitive decline and imminent mortality in patients (Pertovaara et al., 2006). The gradual rise in kynurenate levels probably produces a progressively greater blockade of NMDAR in the CNS causing a generalised disruption of synaptic transmission. Inhibitors of KAT (see below) might slow this cognitive decline.

Recent work suggests a role for quinolinic acid in the accumulation of tau proteins, abnormally hyper-phosphorylated forms of which constitute the microfibrillary tangles which are frequently observed in Alzheimer's disease (Rahman et al., 2009).

Huntington's disease (HD)

Although this condition is often first diagnosed on the appearance of motor symptoms, these are preceded by cognitive abnormalities which can be revealed by appropriate testing. Patients with an increased likelihood of developing this inherited disorder show impaired performance on tasks such as attentional set shifting and semantic verbal fluence (Lawrence et al., 1998). Later work extended this profile to show deficits in pattern and spatial recognition memory, simultaneous and delayed matching-to-sample and aspects of visual working memory (Lawrence et al., 2000). Most of the disturbed cognitive functions are known to involve the striatum, consistent with the later emergence of motor symptoms caused by striatal neurodegeneration.

Early animal models of the disease involved the non-selective destruction of striatal neurons using excitotoxins such as kainic acid. Later, with the recognition that the agonist activity of quinolinic acid at NMDA receptors (Stone & Perkins, 1981) translated into neurotoxicity (Schwarcz et al., 2003), it soon became apparent that quinolinate generated a more selective animal model. Intrastriatal delivery of quinolinic acid produces a profile of neurochemical, electrophysiological and behavioural changes that closely mimic those seen in patients with HD (Beal et al., 1991; Popoli et al., 1994; Shear et al., 1998; Schwarcz et al., 2009).

More recently developed models involve engineering the expression of the abnormal HD protein huntingtin, the sequence of which is terminated by a series of glutamine residues, coded for by cytosine-adenine-guanine (CAG) repeats in the gene. Abnormal huntingtin can form aggregates that ultimately lead to neuronal death. The neuronal damage and behavioural sequelae seen in these animals appear to be mediated through activation of NMDA receptors (Heng et al., 2009). Levels of quinolinic acid and 3HK are increased in the neocortex and striatum and are also increased in human patients (Guidetti et al., 2006), along with activity of their inter-converting enzyme 3HAO (Schwarcz et al., 1988; Pearson et al., 1992; Guidetti et al., 2000). The initial enzyme, IDO is also more active in patients in the more advanced stages of the disease (Stoy et al., 2005). The role of kynurenines may be strengthened by the finding that

3HK can enhance the toxic effects of quinolinic acid (Guidetti & Schwarcz, 1999). In the R6/2 mouse model of Huntington's disease, activity of KMO is also increased (Sathyasaikumar et al., 2010), results which would contribute to the increased conversion of tryptophan to 3HK and quinolinic acid. Intriguingly, quinolinic acid itself can promote the production of huntingtin (Tatter et al., 1995).

This potential involvement of the kynurenine pathway has been strongly supported by the discovery of a correlation between levels of components of the pathway and the length of the triplet codon CAG repeat (Forrest et al., 2010). The codon can be repeated up to 35 times in normal individuals, but if it exceeds 40, most patients exhibit symptoms of the disorder. The correlation between codon repeat number and kynurenine pathway metabolites is one of very few that have been demonstrated between the genetic abnormality and a biochemical parameter. The relationship is strengthened by the fact that the pre-motor cognitive dysfunction also correlates with the CAG repeat length (Jason et al., 1997).

An important discovery was that the kynurenine:tryptophan ratio correlated with levels of the pro-inflammatory cytokine interleukin-23 (IL-23), as did levels of kynurenic acid and anthranilic acid (Forrest et al., 2010). Increased levels of the latter compound had been reported previously in several inflammatory conditions (Darlington et al., 2010). Correlations were also revealed between kynurenine metabolites and blood concentrations of the soluble human leukocyte antigen-G (sHLA-G), an anti-inflammatory molecule. This would be consistent with earlier data that tryptophan and several kynurenine metabolites can induce cell surface and secreted forms of sHLA-G in immune system dendritic cells, leading to their reduced ability to activate T cells. This concept in turn would add to the evidence that several kynurenine metabolites have critical functions within the immune system as well as the nervous system (Stone et al., 2013). Interestingly, since interferon-γ is one of the most potent inducers of IDO and sHLA-G can induce the production of IFN-γ from peripheral blood mononuclear cells, it is likely that sHLA-G produces an indirect activation of the kynurenine pathway. The mechanisms by which IDO and sHLA-G act – separately or in combination – to affect T cell function, and the extent to which

they do so in a manner relevant to the motor or cognitive symptoms of HD, remain unclear. Overall, there are strong arguments for overactivity of these compounds being involved in HD, probably generating cognitive symptoms via the kynurenine pathway. This proposal has been further strengthened by the discovery that expression of abnormal huntingtin in yeast cells can produce cell damage by increasing activity along the kynurenine pathway (Giorgini et al., 2005 ; Stone et al., 2012).

Immune function, kynurenines and cognition

The relationship between kynurenines and immune function may have a wide relevance to 'sickness behaviour' and the lasting effects of infection on motor and cognitive function in conditions such as cerebral malaria (Clark et al., 2005) and trypanosomiasis (Rodgers et al., 2009). Indeed, many features of what is often referred to as 'sickness behaviour' may be linked to kynurenine metabolism, including the anxiety and anhedonia or apathy that seem to be induced by activation of IDO (Salazar et al., 2012). The induction of IDO and KMO by infecting organisms is probably secondary to the increased expression of IFN-γ but may be the mechanism through which infection by viruses can produce cognitive dysfunction. The infection results in altered hippocampal neuron structure and impairs reversal learning in an adaptation of the water maze test of spatial memory (Jurgens et al., 2012).

Activation of the kynurenine pathway is also likely to account for the depression which follows viral or bacterial infections and treatment of patients with interferons (O'Connor et al., 2009; Raison et al., 2010; Dantzer et al., 2008).

Stress

Stress causes cognitive changes and alterations of emotionality (Davidson & McEwen, 2012) which may lead to mental illness (de Kloet et al., 2005). This may occur directly in adults, especially after experiencing chronic stress over many months or years (Marin et al., 2011) but can also appear in later life after the exposure to stress in early postnatal life, with the

appearance of defective memory and executive functioning (Pechtel & Pizzagalli 2011; Hedges & Woon 2011). Indeed, there is good evidence that pre-natal stress in the pregnant female can lead to the emergence of cognitive and emotional problems in the offspring in later life (Lupien et al., 2009).

The negative effect of stress on cognition may be linked to the activation of tryptophan metabolism by TDO (Miura et al., 2011; Kiank et al., 2010). Whereas IDO is rather non-selective in its metabolism of compounds with a basic indole structure, (including 5HT and melatonin), TDO is much more selective for tryptophan and is a high capacity, low affinity enzyme which maintains the blood levels of tryptophan around 60μM. Hence, its importance is primarily to regulate the amounts of tryptophan to which immune system cells in the tissues or cells within the CNS are exposed. The role of TDO may be far more important than often realised since it is induced by glucocorticoids. These adrenal steroids are secreted in response to stress and their induction of TDO can potentially alter the blood levels of kynurenines to a much greater extent than IDO. This, therefore, is another mechanism by which an environmental factor – stress induced by a wide variety of life situations – could modify brain levels of quinolinic acid and kynurenic acid and modulate neuronal activity leading to changes in behaviour and cognitive function, or a susceptibility to external influences arising subsequently.

Exposure to corticosterone can markedly affect NMDAR function (Tse et al., 2012) and may lead to severe and persisting clinical depression and other disorders (Muscatell et al., 2009). For example, repeated stress has adverse effects on temporal order recognition tests (involving the PFC), associated with reduced NMDAR and AMPAR function (Yuen et al., 2012). Whether cognitive function is enhanced or suppressed depends on the amount of steroid present and the relative activation of glucocorticoid and mineralocorticoid receptors (Popoli et al., 2012). Glucocorticoids may affect glutamate receptors particularly in the PFC where they are believed to be crucial in the altered metabolic activity there linked with schizophrenia (Marin et al., 2011).

Post-surgical cognitive recovery

One further example of a link between kynurenines and cognition has emerged from a study of cognitive function in patients after cardiac bypass or major thoracic surgery, which should probably be viewed as major stressors. It is well established that major surgery under general anaesthesia is followed by cognitive deficits that may take months or years to resolve. In a study employing six independent tests of cognitive function, highly significant correlations were established between the levels of kynurenine metabolites and the degree of cognitive impairment tested at three time points after thoracic surgery (Forrest et al., 2011). No comparable correlations were seen between cognition and the levels of pro-inflammatory cytokines. The extent of the correlation was greater than had been noted for any molecular marker of intellectual functioning in previous studies. A similar result was reported more recently in which, for patients recovering from a stroke, the level of kynurenine pathway activation was correlated inversely with cognitive recovery (Gold et al., 2011), a finding which also supports the previously noted correlations between kynurenine pathway activation and the post-stroke infarct size (Darlington et al., 2007).

Kynurenines and brain development

If changes along the kynurenine pathway, whether induced by stress, infection, surgery or other factors, are involved in CNS abnormalities in the adult, the question arises as to whether changes in the pathway early in life, or even prenatally by conditions affecting the pregnant mother, could influence cognitive function or behaviour in the offspring. Factors such as stress or infection could predispose some individuals to develop behavioural abnormalities when exposed to subsequent life events which would have less or no effect on individuals not exposed to those factors. In all these situations, the activation of tryptophan metabolism along the kynurenine pathway induced by steroids, cytokines or other agents released by stress and infection may be the common factor mediating changes in glutamate receptor function.

Prenatal exposure to the viral-mimetic double-stranded RNA complex polyinosinic:polycytidylic acid (poly(I:C)) can selectively alter the expression of a number of

proteins involved in early neurogenesis, axonal guidance and synapse formation in the brains of the postnatal offspring examined 21 days after birth (Forrest et al 2012). The changes observed included decreased expression of the NMDAR subunit GluN1, while subsequent work (unpublished) also indicates changes in the morphogenetic protein sonic hedgehog and α-synuclein levels, combined with an increased expression of tyrosine hydroxylase. Since these effects may involve the activation of the kynurenine pathway, studies were performed on the effects of inhibiting kynurenine production using Ro61-8048.

When pregnant rats were treated prenatally with Ro61-8048, there was a substantial (more than 10-fold) increase in the brain levels of kynurenic acid together with decreased expression of GluN2A subunits and increased GluN2B in the embryo brains after only 5hours, with changes in sonic hedgehog protein after 24h (Forrest et al., 2013). When the offspring were allowed to mature to 21 days of postnatal age (P21), the brains exhibited increased expression of GluN2A, GluN2B and the associated postsynaptic density protein PSD-95. Levels of sonic hedgehog were now increased relative to vehicle-exposed animals, while increased expression of doublecortin and Proliferating Cell Nuclear Antigen (PCNA) suggested increased neurogenesis (Forrest et al., 2013). The overall amounts and ratio between the different glutamate receptor subunits is increasingly considered to be critical in synaptic function, plasticity and neurodegeneration (Hardingham and Bading, 2011). These molecular changes in early brain development were associated with enhanced neuronal excitability in the postnatal offspring and increased long-term potentiation, which is considered critical in some aspects of cognitive function (Forrest et al., 2013).

An important link between these various changes and behaviour is indicated by work showing that the administration of kynurenine to rats during adolescence can lead to impairments in social behaviour in adulthood while identical treatment to adults has no such effect (Trecartin & Bucci 2011). In the related study referred to earlier (Pocivavsek et al., 2012), kynurenine treatment before and immediately after birth produced not only the expected increase in kynurenic acid levels but also produced significant cognitive dysfunction in adulthood, including

abnormal performance in passive avoidance learning and in the water maze spatial learning task.

Nicotinic cholinoceptors

The focus of attention, in the relationship between kynurenines and cognition, continues to be on NMDAR but there is evidence that kynurenic acid may also have effects on α7-homomeric nicotinic receptors (α7NRs) for acetylcholine. Modifications in the expression and function of α7NRs can result in marked changes in some aspects of cognitive behaviour (Deiana et al., 2011; Graef et al., 2011). The septo-hippocampal projections include a substantial cholinergic component in which the release of acetylcholine can activate muscarinic and nicotinic receptors on the target neurones. A similar projection from the nucleus basalis to the neocortex seems to underlie aspects of learning as well as logical thought and reasoning. The α7NRs are involved in cognitive function and may be underactive in schizophrenia (Mexal et al., 2010; Breese et al., 2000), while their deletion has profoundly negative consequences for learning and memory (Hernandez et al., 2010). Conversely, selective agonists at α7NRs can suppress the positive and negative symptoms of schizophrenia, including aspects of cognitive function such as visual recognition, logic and rational thought (Mueller & Dursun, 2011). In the early stages of Alzheimer's disease, nicotinic cholinergic agonists or cholinesterase inhibitors have beneficial effects, restoring some degree of memory and reasoning in the disease and in animal models (Kihara et al., 2001; Ren et al., 2007).

The evidence for a role of kynurenic acid in modulating nicotinic receptor function, however, remains the subject of intense debate. The initial observations were reported using neuronal cultures in which depolarisation was produced by agonists at α7NRs (Hilmas et al., 2001) and kynurenic acid appeared to be more potent an antagonist than at NMDARs. Subsequent work failed to confirm this greater potency in intact brain slices in which kynurenic acid blocked NMDARs and α7NRs with comparable potency (Stone, 2007). The differences between these

conclusions may be related to the presence and access of endogenous glutamate and kynurenic acid itself to sub-synaptic or extra-synaptic sites, which will be more accessible in cell culture than in slices (Ren et al., 2007). Subsequent studies have examined the phenomenon in more detail (Alkondon et al., 2004, 2011) while others have failed to demonstrate any antagonism at α7NRs using concentrations of kynurenic acid which completely block responses to NMDA (Mok et al., 2009; Dobelis et al., 2012). In addition, a study of dopaminergic activation by kynurenic acid (discussed above) concluded that α7NRs were not involved, suggesting that the phenomenon was probably caused exclusively by blockade of NMDARs (Linderholm et al., 2007). Interestingly, the loss of kynurenic acid produced by the deletion of KAT-II was associated with increased sensitivity of α7NRs which was not caused by increased receptor expression (Alkondon et al., 2004). Overall, it is possible that the apparent effects of kynurenic acid on α7NRs may be secondary to the effects of kynurenic acid on NMDARs.

Drug development

It will be clear that there are several approaches to modulating activity along the kynurenine pathway that may have therapeutic potential in the treatment of cognitive disorders. In general, most medicinal chemistry has been focussed on the inhibition of KMO or IDO. In neurodegenerative disorders such as Huntington's disease, the excitotoxic activity of quinolinic acid and the experimental evidence for the importance of this or other metabolites such as 3-HK suggest that inhibition of KMO would be neuroprotective by reducing the generation of these toxins. The continuing development of interest in kynurenine pathway inhibitors, especially for KMO (Cesura & Röver, 1999), is reflected in the growing number of patents being taken for novel series of compounds with acceptable levels of inhibitory activity. These include series of 2-aminobenzoyl compounds (Daily et al., 2010; Zisapel et al., 2012)(Figs. 3A,B), pyrrole derivatives (Della Torre et al., 2001) (Fig. 3C), a variety of 2-amino-4-phenyl-4-oxo-butanoic acid derivatives (Varasi et al., 2001)(Fig. 3D) as well as a range of 5-(3-phenyl-3-oxo-propyl)-

1H-tetrazole derivatives (Pevarello et al., 2000)(Fig. 3E) and 4-phenyl-4oxo-2-butenoic acid derivatives (Giordani et al., 2000) (Fig. 3F). Some of the compounds produced by these latter two groups showed IC50 values less than 1μM against KMO, while three of the series synthesised by Varasi et al., (2001) had IC50s between 140 and 270nM. A different chemical avenue involved the development of cyclopropane-1-carboxylic acids (Benatti et al., 2005) (Fig. 3G).

Most of these patents specify a wide range of potential clinical applications, including neurodegenerative conditions such as Huntington's disease and stroke, while others have focussed primarily on the role of kynurenine pathway involvement in disorders such as Huntington's disease (Muchowski et al., 2011) or on the cerebral side effects of metabolic disorders such as diabetes (Autier et al., 2010). On addition to patenting the concept of examining the kynurenine pathway as a route to the treatment of Huntington's disease (Muchowski et al., 2009), the group generated a series of compounds, several of which inhibited KMO by more than 50% at a concentration of 10μM.

Several multi-compound patents cover compounds designed to inhibit IDO (Andersen et al., 2012) (Figs. 3H,J). Of a large series of compounds the most potent was adociaquinone B (Fig. 3J) with a Ki of 25nM against IDO. The inhibition of IDO may involve actions on both the CNS and immune systems and are more often being considered for their potential anti-cancer properties. IDO is a key player in immune surveillance and its control over infectious organisms and cancer cell removal. Although it is still considered possible that this role of IDO is mediated partly through the local depletion (starvation) of tryptophan concentrations resulting from its activation, it is increasingly thought that downstream metabolites of the kynurenine pathway, especially 3HK and 3HAA are involved, in view of their ability to alter the balance between pro-inflammatory and anti-inflammatory T cell populations such as Th1, Th2 and Th17. In fact, the potential impact of KMO inhibition on the immune system has not yet been explored in depth, so that it is not possible to state whether KMO inhibition would have any deleterious effects on

immune function under basal or challenged conditions, to the extent that these would compromise their therapeutic utility.

In addition, KMO inhibition seems to have little effect on quinolinic acid concentrations, either because of compensatory changes in enzyme expression or activity, or because of the shift to an alternative pathway. The major suspect in the latter case would be the metabolism of kynurenine to anthranilic acid followed by the spontaneous oxidation of this compound to 3HAA and the normal conversion of the latter to quinolinic acid. Interestingly, there is growing evidence that this route is recruited in a range of inflammatory conditions in which the levels of anthranilic acid are increased several-fold above normal levels (Darlington et al., 2010).

KAT inhibition

A different therapeutic approach to the kynurenine pathway lies in the possibility of reducing kynurenic acid levels in order to decrease the overactivity in dopaminergic projections which characterises psychotic disorders such as schizophrenia. Schizoid delusions and hallucinations can also follow the chronic use of psychedelic agents such as cannabis and may develop in the advanced phases of Parkinson's disease treated with dopamine-facilitating agents. Dopaminergic overactivity may be secondary to the hypo-glutamatergic activity caused by increased kynurenic acid concentrations in these various situations.

The simplest practical approach to achieving reliably reduced levels of kynurenic acid *in vivo* would be to lower production by inhibiting KAT, since this not only has the desired effect on kynurenic acid production but seems to create little interference with the rest of the kynurenine metabolic pathway. Simple inhibitors such as L-cysteine sulphinate were described by Kocki et al. (2003), producing substantial inhibition at low micromolar concentrations. Several other relatively non-selective compounds have been shown to have inhibitory activity including the nitric oxide synthase inhibitor L-nitro-arginine (Luchowski et al., 2001), 3-nitropropionic acid and 1-methyl-4-phenyl-pyridinium (MPP+) (Luchowski et al., 2002).

Several groups have subsequently produced more specific chemical structures with high selectivity and potency as KAT inhibitors. One of the first highly specific targeted compounds was (S)-4-(ethylsulfonyl)benzoylalanine (ESBA; Fig. 4A) (Pellicciari et al., 2006) which showed high selectivity against rat KAT with little effect on any of the other enzymes of the kynurenine pathway. When administered to rats, ESBA reduced kynurenic acid levels in the brain and produced a corresponding increase in the release and extracellular concentrations of acetylcholine (Zmarowski et al., 2009), dopamine (Amori et al., 2009) and glutamate (Konradsson-Geuken et al., 2010). In addition to these neurochemical effects, the intracerebroventricular administration of ESBA to rats produced a significantly improved visuo-spatial memory performance in a water maze paradigm (Pocivavsek et al., 2011). Involvement of kynurenic acid in these neurochemical and behavioural effects of ESBA were prevented by the simultaneous administration of kynurenine or kynurenic acid itself. Unfortunately, later work indicated that ESBA was much less active as an inhibitor of the human KAT enzyme because of a higher molecular flexibility in the region of the substrate binding site (Casazza et al., 2011).

A second compound developed as a more potent but still selective inhibitor was (S)-(-)-9-(4-aminopiperazin-1-yl)-8-fluoro-3-methyl- 6-oxo-2,3-dihydro-6H-1-oxa- 3a-azaphenalene-5-carboxylic acid (BFF-122; Fig. 4B) (Rossi et al., 2010). This agent blocks KAT activity of *in vitro* brain slices (Alkondon et al., 2011) and *in vivo* after direct, intrastriatal administration (Amori et al., 2009) but has not been examined in as much detail as ESBA, or in behavioural tests.

Akladios et al., (2012) reported that 6-ethoxy-6-oxo-5-(2-phenylhydrazono) hexanoic acid and 3-(2-carboxyethyl)-1H-indole- 2-carboxylic acid were promising compounds from which to derive novel inhibitors of human KAT-I. Of 12 derivatives described the most active was 5-(2-(4-chlorophenyl)-hydrazono)-6-ethoxy-6-oxohexanoic acid (CHEH; Fig. 4C) which exhibited an IC50 of 19.8 μM. Even this level of activity is sometimes considered inadequate for the development of clinically useful drugs, especially when concentrations comparable with the IC50 must be achieved within the CNS without accompanying side effects that might be produced by the inevitably higher concentrations existing peripherally.

One route to compounds with significantly higher activity may be that pursued by Dounay et al., (2012) who generated the bi-cyclic compound PF-04859989 (Fig. 4D) as a potent and selective inhibitor of human and rat KAT-II with an IC50 of approximately 20nM. X-ray crystal structure and C-13 NMR studies of PF-04859989 bound to KAT-II revealed the formation of a covalent complex between the compound and pyridoxal phosphate, a key co-factor for KAT-II activity. The formation of this adduct effectively blocked activity of the enzyme in an irreversible fashion. A strong advantage of PF-04859989 over previous inhibitors is its ability to penetrate the CNS relatively readily. The same group has now extended the chemical family represented by PF-04859989 with a series of isosteric analogues, also active in the nanomolar range, which retain good penetration into the CNS after systemic administration (Henderson et al., 2013). Although no behavioural data have yet been reported using these compounds, they appear to have a promising, non-toxic profile which could lead to their further development.

Since kynurenic acid acts primarily at the Gly-B-binding site for glycine, acting partly in a competitive manner, the combined use of a KAT inhibitor with a glycine transport inhibitor to increase extracellular levels of glycine could represent an important synergistic approach yet to be tested experimentally.

A number of patents explore the molecular flexibility of blocking KAT using endogenous compounds as inhibitors with potential clinical utility. Some of these are targeted specifically at KAT, including a variety of naturally occurring aliphatic compounds (Guidetti et al., 2008) while others are intended as more general inhibitors of transaminases with the ability to include inhibition of KAT (Teichberg, 2008, 2010). Since most transaminases have limited selectivity for individual enzymes, the overall balance of inhibitory activity is probably similar with these two approaches.

Summary

The kynurenine pathway generates a series of neuroactive compounds, the most prominent of which can modulate the activity of neuronal pathways by altering the degree of activation

(quinolinic acid) or blockade (kynurenic acid) of NMDARs. This review has highlighted some of the disorders for which there is strong evidence implicating the kynurenines in the behavioural and cognitive symptoms. With several enzymes along the route, the kynurenine pathway is eminently suitable for the development of pharmacological interventions to treat and, possibly, to prevent cognitive dysfunction in these and other CNS disorders.

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Figure legends

Figure1

A summary of the major components of the kynurenine pathway for the oxidation of tryptophan.

Figure 2

A summary of the involvement of kynurenines in three groups of CNS cognitive disorders: (A) schizophrenia and related conditions such as autism spectrum disorders (SZ), (B) Huntington's disease (HD) and (C) dementias such as HIV-Associated Neurocognitive Disorders (HAND), with probable relevance to conditions such as Alzheimer's disease. The diagram also illustrates the influences of stress on the kynurenine pathway via the induction of glucocorticoid secretion which induces TDO in the liver, and infections which cause the induction of IDO in several subsets of leucocytes via the action of interferons. The activation of IDO or TDO can produce localised depletion of tryptophan from proliferating cells while increasing the concentrations of kynurenine and its metabolites in tissues. Some of these metabolites such as kynurenic acid and quinolinic acid are active primarily on neuronal function, while 3HK and 3HAA have their main effects on T cell proliferation and cytokine secretion.

Abbreviations:

Glu: glutamate

DAm: dopamine

3HK: 3-hydroxykynurenine

3HAA: 3-hydroxyanthranilic acid

Htt: huntingtin

IDO: indoleamine-2,3-dioxygenase

Kyn: kynurenine

Kyna: kynurenic acid

α7NRs: α7-nicotinic cholinoceptors

Quin: quinolinic acid

TDO: tryptophan-2,3-dioxygenase

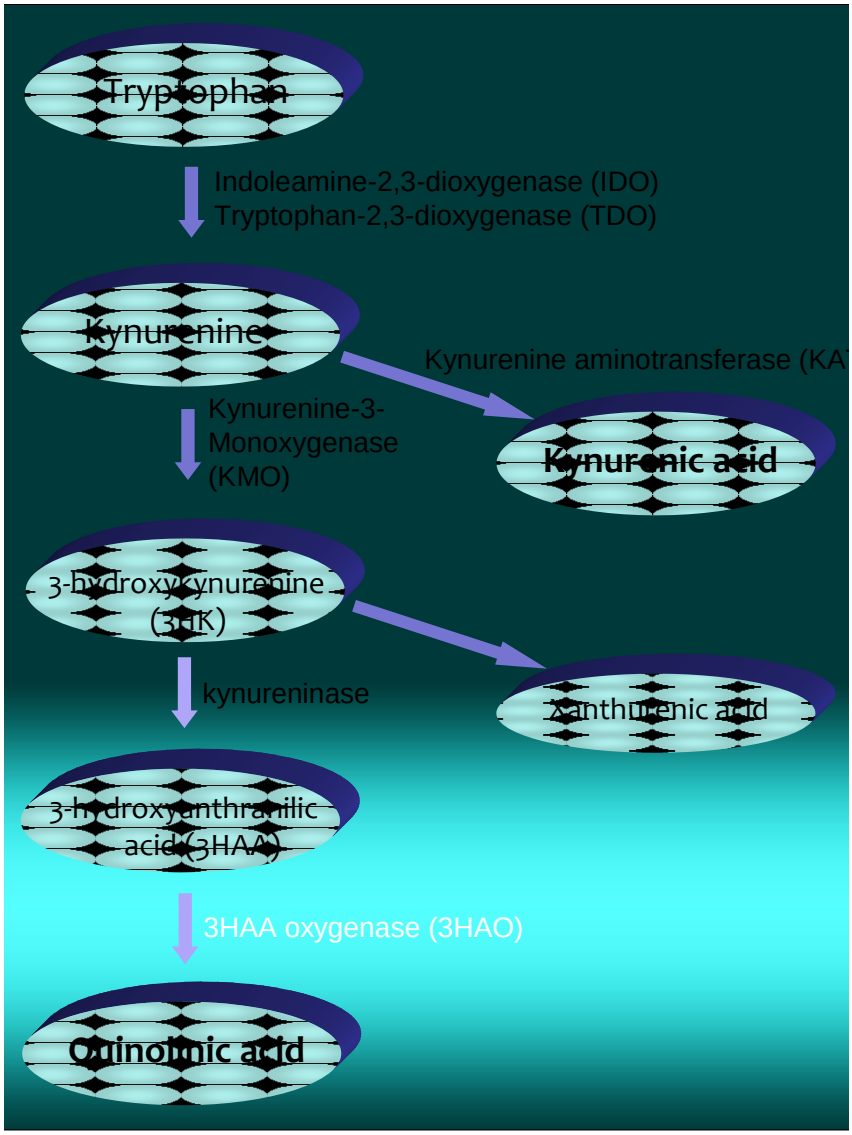
Trp: tryptophan

Figure 3

Structures of compounds described in patents for inhibitors of kynurenine-3-monoxygenase or indoleamine-2,3-dioxygenases targeted as CNS disorders.

Figure 4

Structures of compounds described in patents for inhibitors of kynurenine aminotransferase.



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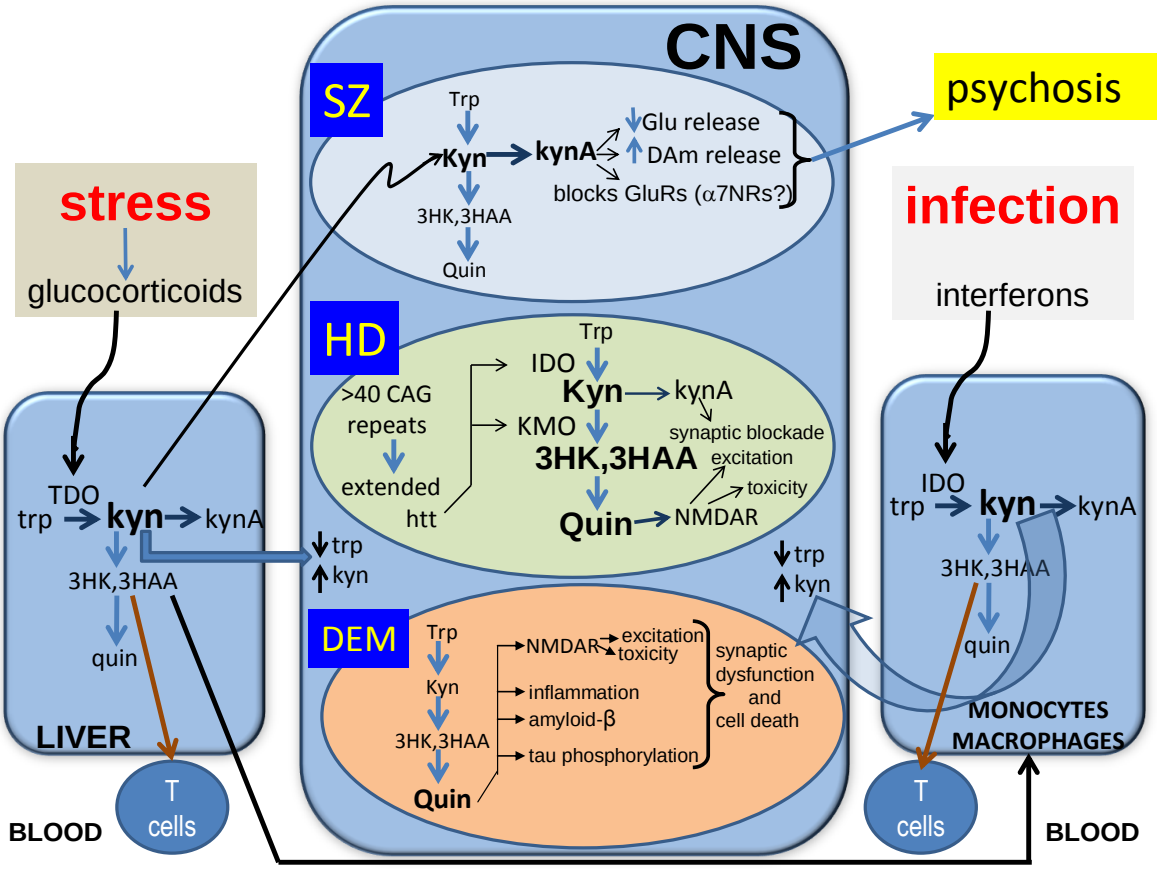

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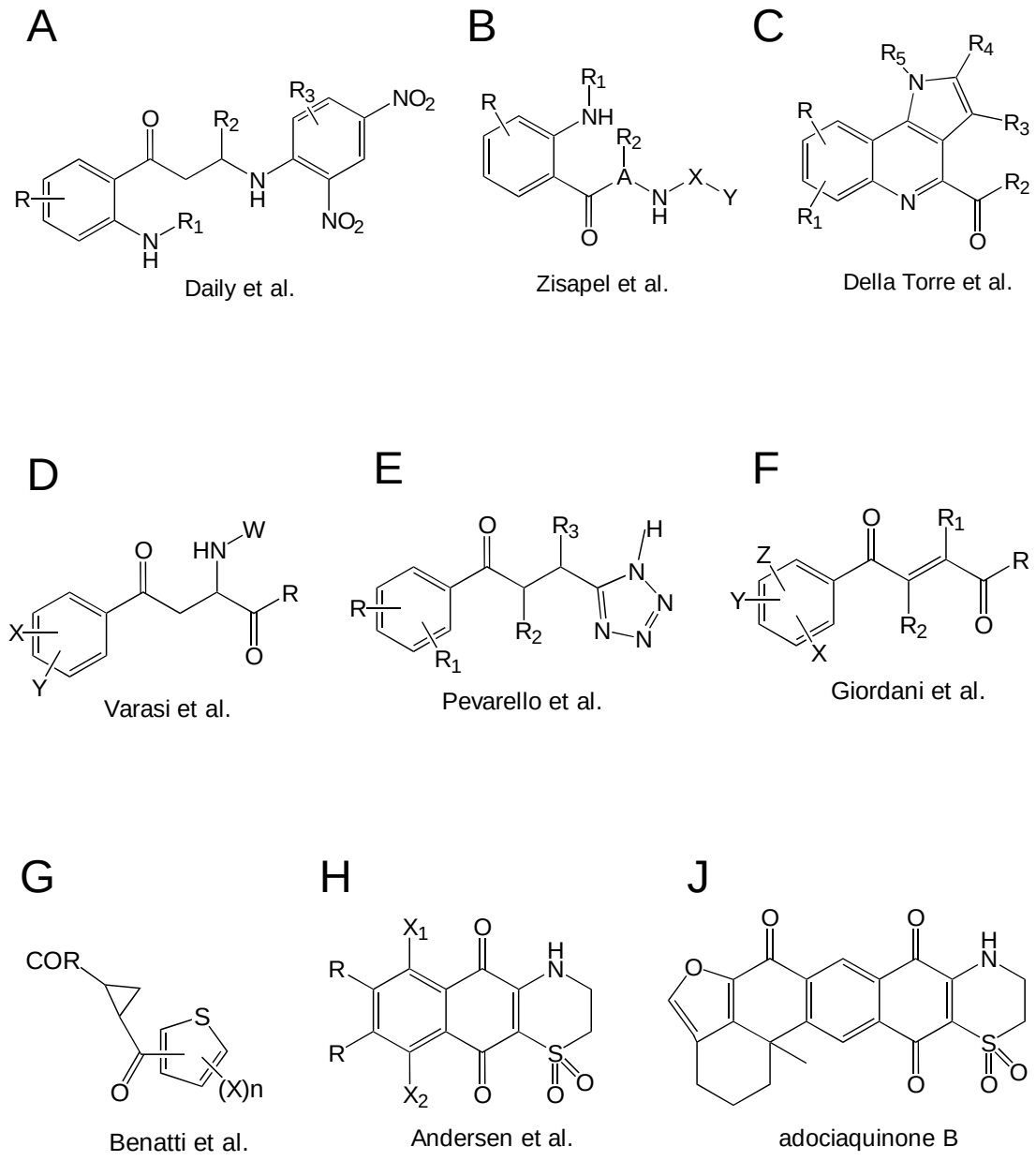

Figure 3

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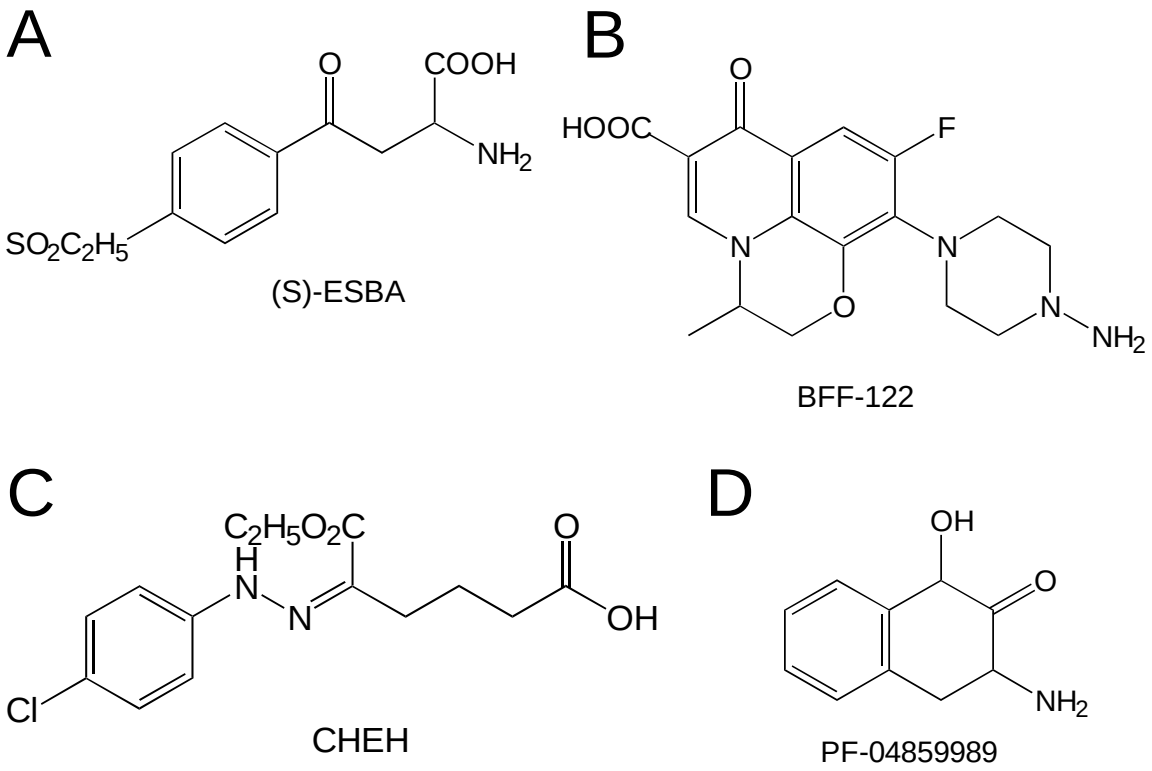

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