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Invited Review

Immunopathogenesis of cerebral malaria

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Abstract

Malaria is one of the most important global health problems, potentially affecting more than one third of the world's population. Cerebral malaria (CM) is a deadly complication of *Plasmodium falciparum* infection, yet its pathogenesis remains incompletely understood. In this review, we discuss some of the principal pathogenic events that have been described in murine models of the disease and relate them to the human condition. One of the earliest events in CM pathogenesis appears to be a mild increase in the permeability to protein of the blood–brain barrier. Recent studies have shown a role for $CD8^+$ T cells in mediating damage to the microvascular endothelium and this damage can result in the leakage of cytokines, malaria antigens and other potentially harmful molecules across the blood–brain barrier into the cerebral parenchyma. We suggest that this, in turn, leads to the activation of microglia and the activation and apoptosis of astrocytes. The role of hypoxia in the pathogenesis of cerebral malaria is also discussed, with particular reference to the local reduction of oxygen consumption in the brain as a consequence of vascular obstruction, to cytokine-driven changes in glucose metabolism, and to cytopathic hypoxia. Interferon-γ, a cytokine known to be produced in malaria infection, induces increased expression, by microvascular endothelial cells, of the haem enzyme indoleamine 2,3-dioxygenase, the first enzyme in the kynurenine pathway of tryptophan metabolism. Enhanced indoleamine 2,3-dioxygenase expression leads to increased production of a range of biologically active metabolites that may be part of a tissue protective response. Damage to astrocytes may result in reduced production of the neuroprotectant molecule kynurenic acid, leading to a decrease in its ratio relative to the neuroexcitotoxic molecule quinolinic acid, which might contribute to some of the neurological symptoms of cerebral malaria. Lastly, we discuss the role of other haem enzymes, cyclooxygenase-2, inducible nitric oxide synthase and haem oxygenase-1, as potentially being components of mechanisms that protect host tissue against the effects of cytokine- and leukocyte-mediated stress induced by malaria infection.

Keywords: Malaria pathogenesis; Cytokines; Immunopathology; Indoleamine dioxygenase; Haem enzymes; Brain metabolism

1. Introduction

Malaria, together with tuberculosis and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), is one of the three most important infectious diseases worldwide in its impact, particularly in terms of morbidity, mortality and deleterious economic consequences. A major, life-threatening complication of malaria infection is cerebral malaria (CM). This condition chiefly afflicts children aged 2–6 years in sub-Saharan Africa and adults in South East Asia. Despite many years of intensive research, the pathogenesis of the condition is not well understood. For example, it is not clear whether the CM in African children is due to the same pathogenetic process as that seen in South East Asian adults. Research carried out to date in human CM and in animal models of the disease indicates that its pathogenesis is complex. Among the factors likely to be involved are human genetics, malaria parasite genetics, nutritional status and intercurrent infections. Evidence from human studies and

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animal models suggests that if there is a host genetic component that influences the outcome of CM, host susceptibility or resistance is likely to be polygenic.

Approaches to studying the pathogenesis of CM are diverse and potentially complementary although, as noted elsewhere (Hunt and Grau, 2003), there traditionally has been a lack of integration between research groups using these different approaches. The best-established approaches are: clinical studies in malaria-endemic areas (e.g. Molyneux et al., 1989); studies of post-mortem material from victims of CM (Brown et al., 1999b); studies with animal models (Grau et al., 1989a,b); genetic predisposition studies in humans or mice (McGuire et al., 1999; Nagayasu et al., 2002). There is presently a heavy emphasis on malaria research in parasite biology, following the sequencing of the *Plasmodium falciparum* genome, which should yield information about anti-malarial drug targets and vaccine strategies. Given that only a small proportion of malaria cases exhibit the complications of severe malaria, and therefore are at risk of death, another reasonable strategy is to identify the key steps in pathogenesis of the complications and identify the specific treatments that block these. Such treatments would be an effective use of scarce health resources in malaria-endemic countries. Currently, as discussed in more detail by Golenser et al. (in press), there is no specific treatment for CM. By understanding its pathogenesis, it may be possible to identify new drug targets in the host that are promising as specific treatments for CM. Another encouraging approach is the possibility of vaccinating against malaria toxins that induce the inflammatory cascade that leads to severe malaria complications (Schofield et al., 2002; Good et al., 2005).

In this review article, we discuss some aspects of the pathogenesis of CM that seem worthy of further attention. In a number of instances, the evidence is based on the use of mouse models of CM so these will be briefly described. *Plasmodium yoelii* and *Plasmodium berghei* ANKA (PbA) cause cerebral syndromes in mice that have numerous similarities to the human condition. The most widely used model is PbA infection of CBA or C57BL/6 mice (Hunt and Grau, 2003; Combes et al., 2005). In some studies, comparisons are made with the pattern of response seen in Balb/C mice infected with PbA, since this strain of mouse is resistant to the cerebral complications seen in CBA and C57BL/6 mice (Combes et al., 2005). Another strain of mouse, DBA/2J, when infected with PbA goes through a phase during which it exhibits both clinical and pathological features of CM but then recovers (Neill and Hunt, 1992).

After parasite inoculation, PbA-infected CBA and C57BL/6 mice show progressive behavioural, histopathological and immunological changes culminating in coma and death around 7 days later (Grau et al., 1986; Thumwood et al., 1988; Neill and Hunt, 1992). Although it is impossible to assert that any animal model of disease is identical to the corresponding human condition, the similarities in behavioural changes, histopathology and immunological manifestations between murine and human CM have become ever more apparent and widely accepted over the last two decades (Grau et al., 1989a,b; Lou et al., 2001; de Souza and Riley, 2002; Hunt and Grau, 2003; Combes et al., 2005). The main distinction is that whereas in human CM it is chiefly, but not exclusively, parasitised red blood cells (PRBCs) that adhere to the cerebral microvascular endothelium (Berendt et al., 1994), in murine CM it is chiefly leukocytes that do so (Neill and Hunt, 1992; Neill et al., 1993), as discussed elsewhere in more detail (Lou et al., 2001; Hunt and Grau, 2003; Combes et al., 2005).

2. Breakdown of the blood–brain barrier in experimental cerebral malaria

Over 30 years ago, Maegraith suggested that oedema might contribute to the pathogenesis of CM (Maegraith and Fletcher, 1971). Conflicting evidence from studies of human disease followed (Sanni, 2001). These are reviewed by Medana and Turner (in press), so will not be discussed here. One observation does deserve comment: treatment of human CM patients with dexamethasone does not aid survival and may even be deleterious (Warrell et al., 1982; Hoffman et al., 1988). At face value this suggests that oedema is not important in human CM. However, in the mouse model, whereas late administration of dexamethasone, after cerebral symptoms have appeared, is ineffective in preventing death from CM, treatment early in the course of disease is completely protective (Neill and Hunt, 1995). This suggests that dexamethasone cannot be an effective treatment in the human disease because it will be administered only after CM is established, which is too late to affect the pathogenetic process.

Studies using a variety of techniques, including measurement of tissue fluid content, Evans Blue (Fig. 1) or radioactive iodine labelling of albumin, immunohistochemical staining for fibrinogen or magnetic resonance techniques, have shown that cerebral oedema does occur in murine CM (Thumwood et al., 1988; Chan-Ling et al., 1992; Neill et al., 1993; Piguet et al., 2000; Penet et al., 2005). Furthermore, a subtle but identifiable increase in vascular permeability to protein occurs in the CNS very early in infection, well before any clinical signs are obvious (Chan-Ling et al., 1992). Endothelial cells in the CNS microvasculature show signs of damage during the progression of murine CM (Neill et al., 1993) and it appears that $CD8^+$T cells may impair the function of these microvascular endothelial cells via perforin-mediated mechanisms, but not through Fas/FasL interaction (Potter et al., 1999, 2006a,b; Nitcheu et al., 2003). The Fas/FasL system is, however, important in CM, possibly mediating the damage to astrocytes that is seen in the mouse model (Fig. 1) (Potter et al., 1999, 2006a,b). The role of $CD8^+$T cells in CM (Yanez et al., 1996; Belnoue et al., 2002; Nitcheu et al., 2003) is discussed in greater detail by Rénia et al. (in press).

The significance of changes in the blood–brain barrier (BBB) in CM is that they would allow cytokines and malaria antigens to enter the brain compartment, from which they normally are excluded. These could lead to the activation of microglia (Fig. 2) or damage to astrocytes (Fig. 1), which have been observed in murine and human CM (Medana et al., 1996, 1997a,b; Ma et al., 1997; Schluesener et al., 1998; Deininger

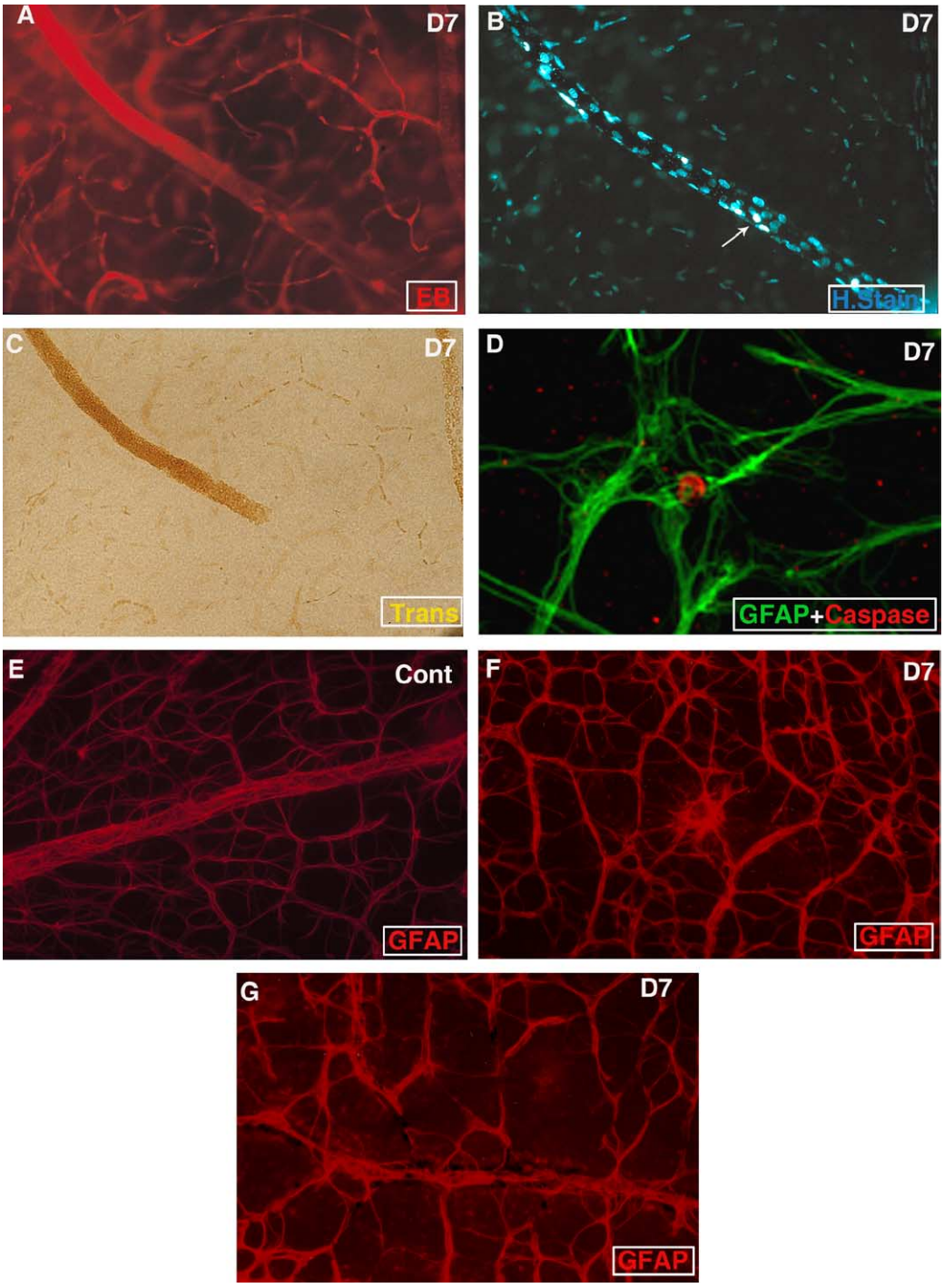

Fig. 1. Vascular and perivascular changes in murine cerebral malaria (CM). (A–D) Retinal wholemount preparations from mice on day 7 p.i. with *Plasmodium berghei* ANKA (PbA). Using the modified Trichrome technique, mice were injected with Monastral Blue followed by a mixture of Evans Blue, which binds to plasma albumin, and bis-benzimide, a DNA marker which stains all nuclei. By examining the same field of view using filters to demonstrate Evans Blue (A), bis-benzimide (B) and transmitted light (C), it is possible to demonstrate an association between monocytes and obstruction to erythrocytes, and plasma perfusion, and breakdown of the blood–retinal barrier. (A) The cessation of plasma flow and plasma leakage in the vessel crossing the field are evident with visualisation of Evans Blue. Leakage of plasma, particularly evident in the upper left segment of the vessel, has resulted in high background fluorescence in this field of view. (B) The nuclei of endothelial cells and monocytes are evident. A cluster of monocytes (arrowed) is seen at the point where plasma flow (A) and erythrocyte flow (C) are obstructed. (D) Green fluorescent staining of glial fibrillary acid protein (GFAP) shows astrocyte processes and red staining shows activated caspase-3 in the cell body. Thus, the astrocyte is undergoing apoptosis. (E–G) Red fluorescent staining of GFAP demonstrates retinal astrocytes. (E) Regular distribution of astrocytes in a normal uninfected CBA mouse retina. Note regular ensheathment of the vessel wall by $GFAP^+$ processes. (F) 5 days p.i. with PbA, astrogliosis is evident in the centre of the field of view. (G) By 7 days p.i., a loss of regular ensheathment of the vessel wall is clearly evident with some vessel segments without any glial ensheathment by astrocytes. Accumulation of Monastral Blue intraluminally in this vessel segment indicates increased adhesiveness, while extravasation of Monastral Blue indicates sites of frank haemorrhage. Images A–C are reprinted from Am J Pathol 140, 1121–30, 1992 with permission from the American Society for Investigative Pathology.

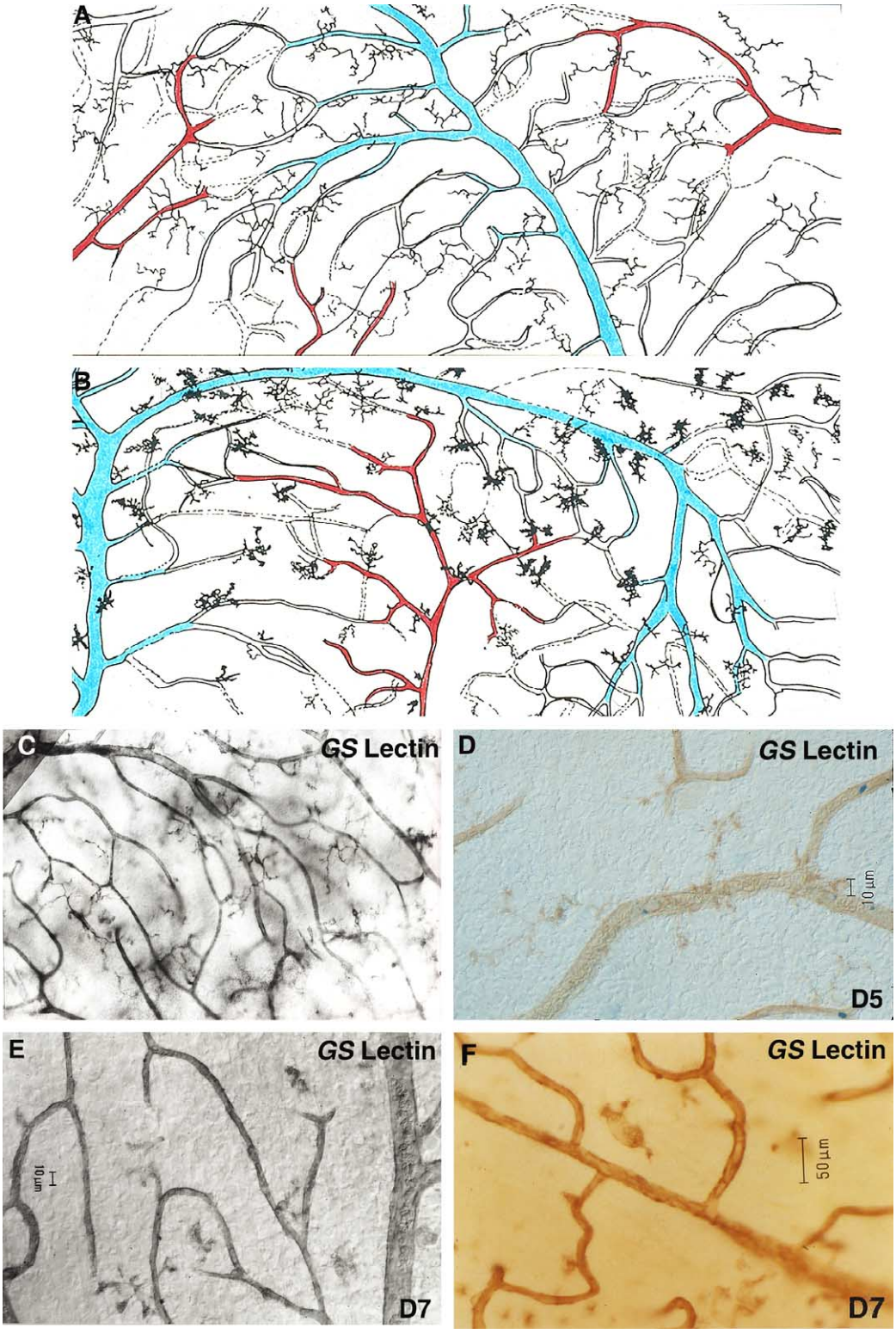

Fig. 2. Redistribution and activation of retinal microglia in murine cerebral malaria (CM). (A and B) Tracings of photographic montages showing the distribution of nucleoside diphosphate-labelled microglia in relation to the retinal vasculature. (A) In control CBA uninfected mice, ramified microglia within the retina were evenly distributed throughout. (B) At the terminal stage of CM, in CBA mice on day 7 p.i. with *Plasmodium berghei* ANKA (PbA), microglia with an activated morphology were concentrated within the vicinity of major retinal veins. The arteries are the narrower calibre vessels coloured red, and the veins are the wider calibre vessels coloured blue. (C–F) Microglia identified with *Griffonia simplicifolia* lectin staining. (C) Normal, ramified microglia in an uninfected CBA mouse. (D) By day 5 p.i. microglia show retracted processes and enlarged somas in focal regions. (E and F) Different morphologies of microglia in PbA-infected mice at day 7 p.i. Microglia generally show a reduced degree of ramification, stout processes and enlarged somas. Images A, B reprinted from Glia 19, 91–103, 1997 with permission.

et al., 2000, 2002). Impairment of astrocyte function would disrupt neuronal activity and production of inflammatory mediators by microglia might contribute to this disruption. A cytokine mediator of inflammation that has been shown (Engwerda et al., 2002) to be necessary for murine CM is lymphotoxin-α (LTα), though the cell of origin is not clear. The involvement of other potential immune system effector molecules such as reactive oxygen species (ROS) and nitric oxide (NO), once thought to be important in causing the pathogenesis of CM, has been questioned (Senaldi et al., 1992; Kremsner et al., 1993; Anstey et al., 1996; Favre et al., 1999; Sanni et al., 1999; Lopansri et al., 2003).

We propose that there are several potential interactions between circulating leukocytes, the BBB and the activation of astrocytes and microglia. It is suggested that activation of microglia to express FasL (Badie et al., 2000), followed by migration of those cells towards the vessels in the CNS (Medana et al., 1997a), could lead to engagement with Fas expressed on astrocytes (Choi et al., 1999) and, thus, damage to the latter cells (Potter et al., 2006a,b). Astrocytes are critical in regulating the interstitial fluid milieu, contributing to maintenance of the BBB and, as discussed further below, they synthesise the neuroprotectant molecule kynurenic acid (KA). Thus loss of astrocytes, or interference with their normal properties, would adversely affect neuronal function.

3. Brain metabolism in cerebral malaria

There are two major theories to explain the pathogenesis of human CM. The ‘mechanical obstruction’ hypothesis suggests that CM is a consequence of the adherence of PRBCs to the cerebral microvascular endothelium, leading to vascular obstruction and cerebral hypoxia (Berendt et al., 1994). The ‘cytokine’ theory assigns a central role to an immunopathological process involving cytokines such as interferon-γ (IFNγ) and tumour necrosis factor (TNF) (Clark and Rockett, 1994). The relative merits of these theories have been extensively debated. Conciliatory hypotheses have been advanced that acknowledge both the importance of cytokine-mediated mechanisms and the role of PRBCs in ‘focussing’ the reaction in the brain (Clark and Cowden, 1999).

In human CM, both in adults and children, lactate increases in the blood and (CSF) (White et al., 1985; Warrell et al., 1988; Molyneux et al., 1989), consistent with the concept of vascular obstruction in the brain leading to tissue hypoxia. However, while oxygen consumption in the brain is reduced, oxygen administration to CM patients does not improve their level of consciousness and their cerebral blood flow, overall, is within the normal range (Warrell et al., 1988). Of course, regional changes in blood flow might be compensated for by increases in collateral blood flow, which would result in apparently normal overall blood flow that masks the regional deficiencies. Other hypotheses to explain the increase in lactate are certainly tenable, in particular that cerebral oxidative metabolism might be inhibited without oxygen delivery being impaired (Warrell et al., 1988). Increased lactate in the CSF is common in adult and paediatric neurological disorders, even those in which vascular obstruction is unlikely to be involved (Auld et al., 1995; Ashwal et al., 1997). Cytokines are thought to be involved in the pathogenesis of human CM (Grau et al., 1989a,b; Clark and Rockett, 1994) and some of these, for example TNF, can influence glucose metabolism in ways that partially mimic a hypoxic response, as discussed below. A high concentration of plasma TNF is a predictor of lactataemia in severe malaria (Krishna et al., 1994).

Recently it has become clear that the mouse model of CM can be used to investigate the mechanisms underlying the change in metabolic profile of the brain in CM (Rae et al., 2004). Significant increases in mouse brain lactate, pyruvate, glutamine and alanine occur in CM but not in severe malaria in the absence of brain involvement (Sanni et al., 2001; Rae et al., 2004). These are consistent with the changes in blood and CSF pyruvate and lactate previously reported in human CM (White et al., 1985; Warrell et al., 1988; Molyneux et al., 1989) and are not a consequence of inadequate glucose uptake into the brain (Warrell et al., 1988; Molyneux et al., 1989; Rae et al., 2004). CNS microvascular obstruction, apparently initiated by monocytes, can be visualised in murine CM (Fig. 1) (Chan-Ling et al., 1992), though it is not widespread. A recent elegant magnetic resonance study demonstrated reduced blood flow in experimental CM, together with elevated brain lactate and reduced high energy phosphates (Penet et al., 2005), consistent with a similar study showing decreased blood flow (Kennan et al., 2005). Interestingly, the metabolic changes in human and experimental CM (increased lactate, glutamine and decreased glucose use) have strong parallels with those seen in vasospastic reaction following sub-arachnoid haemorrhage, which in the latter case are directly correlated with the Glasgow Coma Scale score (Dunne et al., 2005). Recovery from the vasospasm in terms of brain function appears good, albeit there is difficulty in divorcing the vasospastic recovery from the damage caused by the stroke.

Evidence from other diseases suggests that cytokines could contribute to the biochemical changes in the CNS in CM. In experimental meningitis in rabbits, lactate concentration in the brain increases ~4-fold over 22 h (Guerra-Romero et al., 1992). This was suggested to be mediated by TNF (Tureen, 1995), since injection of this cytokine intra-cisternally both decreased cerebral oxygen uptake and increased CSF lactate in rabbits. TNF is produced by brain parenchymal cells during murine CM (Medana et al., 1997b). A similar role for LTα is feasible, and the gene for the cytokine is expressed within the brain parenchyma at the terminal stage of murine CM (Engwerda et al., 2002; Rae et al., 2004). In several types of cultured cell, TNF causes a shift from tricarboxylic acid cycle activity to glycolysis (Tracey and Cerami, 1990; Taylor et al., 1992; Zentella et al., 1998) and in some cases decreases oxygen consumption (Zentella et al., 1998). In Sertoli cells, the cytokine increased the activity of the A isoform of lactate dehydrogenase (Nehar et al., 1997), the mass action potential of which would favour formation of lactate from pyruvate.

Recently, a concept has evolved that might be relevant to brain metabolic changes in malaria infection. The term ‘cytopathic hypoxia’ was coined to describe the situation in

which oxygen supply to a cell or tissue is adequate but oxygen use is subnormal (Fink, 2002). Its characteristics include activation of the nuclear enzyme poly(ADP-ribose) polymerase (PARP), leading to depletion of mitochondrial nicotinamide adenine dinucleotide $(NAD)^+$/NADH. The normal function of PARP is DNA repair (Fink, 2002). A number of factors thought to be involved in the pathogenesis of CM, namely IFNγ, TNF, excitatory amino acids, neuroexcitotoxins and vascular obstruction, can activate PARP (Love et al., 1998, 1999; Cosi et al., 2000; Abdelkarim et al., 2001; Khan et al., 2002; Chiarugi and Moskowitz, 2003). A role for cytopathic hypoxia in CM would be consistent with observations in the human disease that overall cerebral blood flow is not markedly decreased whereas oxygen utilisation is lower than normal (Warrell et al., 1988). Activated PARP is seen in the brains of human malaria victims, although not specifically associated with CM (Medana et al., 2001). Lower NAD^+/NADH levels and decreased mitochondrial function are observed in CM in the mouse (Sanni et al., 2001; Rae et al., 2004). Thus, it has been proposed (Clark and Cowden, 2003; Hunt and Grau, 2003; Rae et al., 2004) that PARP activation and cytopathic hypoxia might be an important determinant of tissue metabolic changes in CM. However, in preliminary studies we have found that $PARP^{-/-}$ mice are not protected against CM (Combes, Parekh, Hunt and Grau, unpublished observations), although they are protected in a cerebral ischaemia model system (Eliasson et al., 1997).

High concentrations of lactate in the CNS are associated with a poor outcome in various neurological disorders (Ashwal et al., 1997). This may simply reflect a metabolic change consequent upon stress induced by various types of damage. However, lactate also may feed the impairment of CNS function in other ways, for example by inducing cytokine production from microglia (Andersson et al., 2005).

Overall, the evidence is consistent with vascular obstruction, cytokine-driven changes in metabolic activity, or both, being responsible for the increased CNS lactate that is indicative of a poor prognosis in human and murine CM. Settling this issue would be relevant to the development of potential therapies.

4. The kynurenine pathway of tryptophan metabolism in malaria

The kynurenine pathway has been assigned key physiological roles in control of reproduction and central regulation of blood pressure. In addition to neurodegenerative disorders of unknown or genetic origin, the adverse effects on the CNS of kynurenine metabolites such as quinolinic acid (QA) have been shown to mediate some of the deleterious effects of infectious agents such as HIV (Heyes et al., 1991). Most recently, the demonstration that this pathway plays a major role in immunomodulation (Mellor and Munn, 1999) has moved it to centre stage in several, often apparently unrelated, physiological and pathophysiological settings. Several compounds derived from this pathway have potent biological activities. Notably, QA is a ligand of excitatory *N*-methyl-D-aspartate (NMDA)

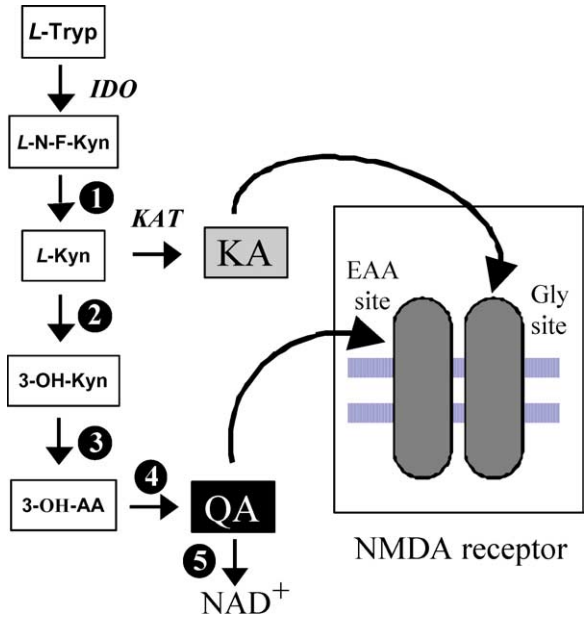

Fig. 3. Kynurenine pathway of tryptophan metabolism in the CNS. L-Tryp, L-Tryptophan; L-*N*-F-Kyn, L-*N*-formyl-Kynurenine; L-Kyn, L-Kynurenine; 3-OH-Kyn, 3-hydroxykynurenine; 3-OH-AA, 3-hydroxyanthranilic acid; EAA, excitatory amino acid; NMDA, *N*-methyl-D-aspartate; Gly, glycine. Enzymes (encircled): (1) kynurenine formylase; (2) kynurenine 3-hydroxylase; (3) kynureninase; (4) 3-OH-AA oxygenase; (5) quinolinate phosphoribosyltransferase.

receptors on certain neurons (Fig. 3) and, at elevated concentrations, can cause neuroexcitotoxic damage (Stone et al., 2001). Its physiological role remains to be established. Also produced from the kynurenine pathway is KA, an antagonist of ligands of the NMDA receptor (Stone et al., 2003). Whereas QA acts through the excitatory amino acid acceptor site on the NMDA receptor (Schurr and Rigor, 1993; Stone et al., 2001), KA acts through the glycine binding site to inhibit the excitatory actions of glutamate, NMDA and kainic acid (Fig. 3) (Perkins and Stone, 1982; Stone et al., 2003). Thus, the kynurenine pathway of tryptophan metabolism generates both a potential neuroexcitotoxin (QA) and a neuroprotectant (KA) and the balance between the levels of these molecules is critical in determining the consequences of activation of this pathway.

Quinolinic acid can damage neurons in vivo and in vitro (Stone et al., 2001). In part, its actions may be linked to the generation of reactive oxygen species and induction of lipid peroxidation (Stone et al., 2000, 2001, and 2003). In addition to its direct actions, QA can potentiate the neurotoxic effects of several glutamate receptor agonists, including NMDA, glutamate and kainic acid (Schurr and Rigor, 1993). As well as these effects exerted via NMDA receptors, QA can induce mitochondrial dysfunction (Stone et al., 2003) and causes increased permeability of the BBB to plasma proteins (St'astny et al., 2000). Balancing these potentially deleterious effects of QA is the fact that it can be further metabolised to NAD^+ (Fig. 3), which might be important when NAD^+/NADH is depleted in conditions of oxidative stress (Grant et al., 2000) or

hypoxia. Furthermore, other metabolites of the pathway have antioxidant activity (Christen et al., 1990).

The first, and rate-limiting, enzyme in the kynurenine pathway is indoleamine 2,3-dioxygenase (IDO) (Fig. 3). Its activity in the CNS is normally very low. By far the most active inducers of expression of the IDO gene are IFNγ and TNF (Taylor and Feng, 1991; Fujigaki et al., 2001). Induction of IDO in endothelial cells by IFNγ has been shown to inhibit the growth of various infectious agents, including *Toxoplasma* (Daubener et al., 2001) and *Staphylococcus aureus* (Schroten et al., 2001). Under normal conditions, about 20% of kynurenine in the brain is derived from local synthesis and 80% from the blood. During localised immune system activation in the brain caused by intrathecal endotoxin injection, all the kynurenine and QA in the brain is the product of local synthesis, presumably consequent upon IDO expression and activity (Kita et al., 2002). Endothelial cells are capable of metabolising tryptophan to kynurenine but not to the later metabolites in the pathway (Stocker and Hunt, unpublished data). Although there are some conflicting reports in the literature, the balance of opinion is that astrocytes can generate kynurenine and KA, but little QA, whereas local microglia or recruited macrophages in the brain can convert kynurenine to QA (Guillemin et al., 2001).

The pathogenesis of experimental CM is dependent on IFNγ (Grau et al., 1989a,b; Yanez et al., 1996). Since this cytokine is the most powerful inducer of IDO activity (Taylor and Feng, 1991), we investigated the possible involvement of the kynurenine pathway in the mouse CM model system (Sanni et al., 1998). We found that IDO activity is dramatically increased in the brains of mice infected with PbA at the terminal stage of CM but also, late in the course of infection, in mice infected with a different parasite (*P. berghei* K173, PbK) that does not cause cerebral involvement. However, the critical ratio of QA:KA (neuroexcitotoxin:neuroprotectant) is significantly increased, by 2-fold, only in experimental CM (Sanni et al., 1998). It, therefore, is possible that this imbalance contributes to the neurological symptoms, and perhaps the morbidity, of CM. The endothelium is the major location of IDO expression in murine malaria (Ball et al., 2002; Hansen et al., 2004). Strong endothelial expression of IDO is seen in PbA infection on day 6 p.i., much lower expression in PbK infection at the same time point, and very strong expression in PbK infection at the terminal stage, correlating with activity measurements in the brain (Sanni et al., 1998). Indoleamine dioxygenase expression is seen in endothelial cells in all organs examined.

Quinolinic acid concentration and the QA:KA ratio are substantially increased in the CSFs of Vietnamese adults with severe malaria compared to UK controls (Medana et al., 2002b). Although both parameters are significantly associated with a fatal outcome, this association is lost when renal function is taken into account. Thus, a substantial portion of the QA may be derived from the blood, due to increased levels consequent upon renal failure, rather than being synthesised within the CNS. However, IDO expression in the brain in human CM has not been evaluated to date. In Malawian children, QA concentration again is significantly associated with fatal outcome and this is not related to renal function (Medana et al., 2003). Quinolinic acid is increased in the CSF of Kenyan children with CM, but KA and renal function were not reported on (Dobbie et al., 2000). Thus, substantial changes in kynurenine pathway metabolites are seen in the CNS in severe and cerebral malaria in three human patient populations.

Intravascular infections such as malaria possess the prominent and distinctive feature of having increased levels of circulating leukocytes that are activated for the production of potentially deleterious substances, such as ROS (Stocker et al., 1984; Descamps-Latscha et al., 1987). Circulating cytokine concentrations also are high. Thus, there is the possibility of activation of perivascular macrophages and the potential for damage to vessels and perivascular tissue in the brain and other organs. We propose that induction of IDO expression in malaria infection, and therefore activation of the kynurenine pathway, is a host protective mechanism mediated by the biologically active products of the pathway (Fig. 4).

Circulating levels of IFNγ are increased in PbA (Hansen, A.M. 2002. Immunological aspects of murine cerebral malaria. PhD Thesis, University of Sydney; Hansen et al., 2003) and PbK (Hansen, A.M. 2002. Immunological aspects of murine cerebral malaria. PhD Thesis, University of Sydney) infections, with higher concentrations being seen in the former infection. Activated $CD8^+$T cells, which play an essential role in murine CM (Belnoue et al., 2002), are one possible source of the IFNγ and natural killer T cells are another (Hansen et al., 2003). Activation of IDO in the endothelium is seen in both PbA and PbK infections (Hansen et al., 2004), eventually reaching higher levels in the latter because the mice die much later since they do not develop CM. Kynurenine may diffuse into the brain parenchyma where it would be converted by microglia and astrocytes to various metabolites (Schwarcz et al., 1983), including some with antioxidant activity (Christen et al., 1990). This would be a beneficial response for the host in conditions of oxidative stress, which conceivably could occur in CM through ischaemia-reperfusion processes (Friberg et al., 2002). Metabolism of tryptophan to NAD^+ could be a significant pathway of NAD^+ replenishment in malaria infection. Brain NAD^+ is depleted in murine CM (Sanni et al., 2001) and this might contribute to the mitochondrial dysfunction seen at the same time (Sanni et al., 2001; Rae et al., 2004). Systemic hypoxia secondary to anaemia would be a stressor of tissue NAD^+ in non-cerebral severe malaria (PbK infection) also, but this might be fully compensated for by activation of the kynurenine pathway, since total brain NAD level is normal in PbK infection (Sanni et al., 2001).

These processes would be protective of host brain function in most malaria infections, as exemplified by PbK infection, as long as increased KA production kept pace with increased QA production so that the neuroexcitotoxic effects of the latter were nullified. The ratio of QA:KA in the brain does indeed remain unchanged in PbK infection, despite increased production of both metabolites (Sanni et al., 1998). Thus, activation of the kynurenine pathway in the endothelium in malaria infection may be a host protective response.

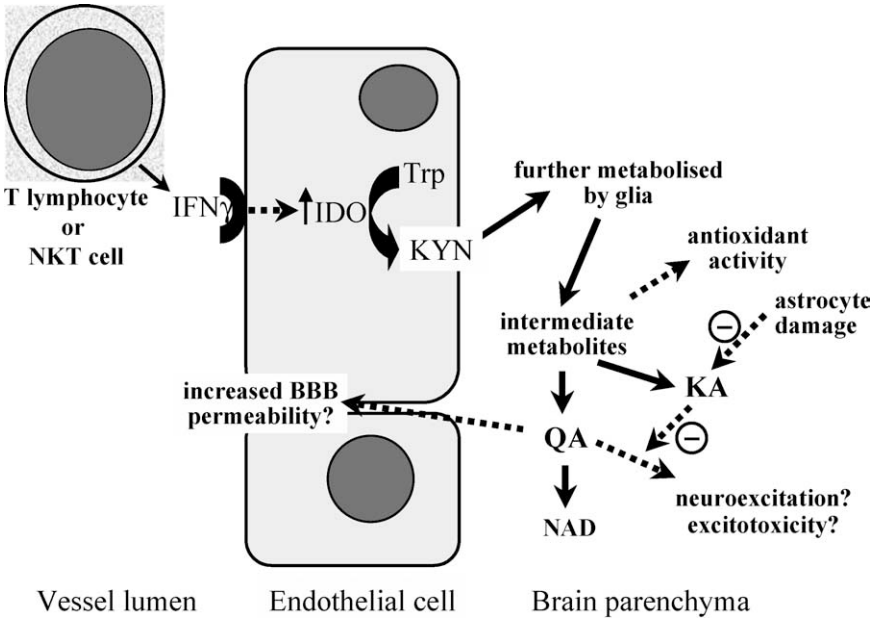

Fig. 4. Possible protective and deleterious effects of kynurenine pathway in the CNS in malaria infection. NKT, natural killer T cell; IFNγ, interferon-γ; IDO, indoleamine 2,3-dioxygenase; Trp, tryptophan; KYN, kynurenine; KA, kynurenic acid; QA, quinolinic acid; NAD, nicotinamide adenine dinucleotide; BBB, blood–brain barrier. Solid arrows are pathways, broken arrows are influences. Negative signs indicate negative effects. NKT cells or $CD8^+$T lymphocytes produce IFNγ, which induces expression of IDO in endothelial cells in the brain (shown here) and elsewhere. IDO converts tryptophan to L-kynurenine, which diffuses into the brain parenchyma and is further metabolised by glia to various metabolites. Normally, the increased QA and KA are in balance. Tissue protective functions are the antioxidant activity of some metabolites and the increased formation of NAD. Potentially damaging changes in CM are related to astrocyte injury. Astrocytes are the chief source of KA, so when damaged there is an excess of QA which may cause neuronal excitation and/or damage and contribute to increased permeability to macromolecules of the BBB.

In murine CM, KA production does not increase sufficiently to maintain the QA:KA ratio (Sanni et al., 1998). The increased QA:KA ratio in CM might contribute to the observed convulsions and hyperactivity and to neuroexcitatory damage. Axonal damage is seen in human (Medana et al., 2002a,b) and murine (Ma et al., 1997) CM. In PbK infection, there is no change in the QA:KA ratio (Sanni et al., 1998) and no obvious neuronal damage. Astrocytes, which are a major source of KA production, are damaged in murine CM (Medana et al., 1996) and this might explain the increased QA:KA ratio in PbA infection and the consequences thereof.

5. Haem enzymes in the host response to malaria

The possible involvement of the haem enzyme IDO in the host response to malaria infection was discussed in Section 4. At least three other haem enzymes, namely cyclooxygenase-2 (COX-2), inducible NO synthase (NOS2) and haem oxygenase-1 (HO-1), also may be relevant. Haem enzymes play numerous roles in homeostasis, immune system modulation, regulation of cellular processes and host protection against environmental insults. They are a diverse group of proteins that contain haem as part of their structure. A number of them are induced in inflammation or oxidative stress and there is evidence that the products of their pathways can regulate the activity of the other induced enzymes (Fig. 5). Expression of COX-2, IDO, NOS2 and HO-1 can all be induced by cytokines and, in addition, hypoxia or haem can induce HO-1 expression. There is also cross-talk between the haem enzyme pathways: for example, in many cell types NO, a product of NOS2, increases expression of COX-2 and HO-1 (Han et al., 1990; Motterlini et al., 2000). NO also inhibits the activity of IDO (Thomas et al., 1994).

The properties of this group of haem enzymes suggest that they might be part of a cassette of host protective mechanisms that is engaged during malaria infection to counteract the potentially deleterious effects of the unique combination of circulating haem, cytokines and activated leukocytes. Relatively little research has been done on the important topic of tissue protective responses against damage induced by malaria infection.

Haem oxygenases catalyse the first and rate-limiting step in the degradation of haem to yield biliverdin-IX, free divalent iron and CO. Haem is toxic to both the malaria parasite and host. The release, through haemolysis of red blood cells, of haem-containing compounds resulting from haemoglobin degradation is a feature of malaria. HO-1 is induced by stimuli such as haem, cytokines, heat shock and NO and is considered to be a cellular defence mechanism. HO-$1^{-/-}$ mice have an increased susceptibility to oxidative stress (Poss and Tonegawa, 1997). In contrast, overexpression of HO-1 is protective in diverse disease models such as cerebral ischaemia and lung injury due to hypoxia or hyperoxia (Panahian et al., 1999; Otterbein et al., 1999a,b; Minamino et al., 2001). HO-2 is highly expressed constitutively in the brain and is important in protecting neuronal cells from apoptosis during cerebral ischaemia (Dore et al., 2000).

The protective effect of HOs may be mediated by the removal of haem, the antioxidant activity of biliverdin/bilirubin, actions of CO on vessels or platelets or the sequestration of iron (which can potentiate free radical formation) by ferritin (Maguire et al., 1982; Stocker et al., 1987; Balla et al., 1992; Ryter et al., 2002; Morisaki et al., 2002; Baranano et al., 2002). These protective mechanisms are potentially highly relevant to the pathogenesis of malaria infection. HO-1 was detected by immunohistochemistry in the brains of only a subset of CM cases in African children, often associated with intravascular monocytes (Clark et al., 2003a). However, in another study of human CM, HO-1 expression was frequently seen in monocytic cells and microglia, often associated with haemorrhages (Schluesener et al., 2001).

Cyclooxygenase-2 is an enzyme originally thought to be induced only in inflammatory situations but later work has shown constitutive expression in some tissues, including the brain. Cyclooxygenases catalyse the formation of prostanoids from arachidonic acid. Prostanoids are potent mediators of a range of inflammatory responses including vasodilation, fever and pain (Tilley et al., 2001). COX-2 mRNA expression is up-regulated in murine CM (Ball et al., 2004) and the protein is found, along with HO-1, in Durck's granulomas in human CM (Deininger et al., 2000; Schluesener et al., 2001). These changes may represent host tissue protective responses that, in the event, are insufficient to prevent CM. A non-selective COX inhibitor (aspirin) shortens the survival time of mice infected with PbA (Xiao et al., 1999); however, that study did not demonstrate that death was in fact due to CM. Salicylates were suggested to contribute to the complications of severe malaria in Kenyan children (English et al., 1996); however, the mechanism of their action is a subject of debate (Clark et al., 2001). Peripheral blood mononuclear cell levels of COX-2 mRNA and protein, and plasma concentrations of a stable metabolite of prostaglandin E2, were lower in Gabonese children with malaria than in a similar group of uninfected children (Perkins et al., 2001). Celecoxib, a selective inhibitor of COX-2, hastens the onset of the fatal cerebral complications in murine CM (Ball et al., 2004). Together, the evidence from mouse studies suggests that a product of the cyclooxygenase pathway might play a partially protective role against tissue complications in malaria. These results, and the involvement of 15-lipoxygenase products of arachidonate metabolism in TNF-induced apoptosis of endothelial cells (Sordillo et al., 2005), suggest that the role of lipoxygenases in the pathogenesis of CM would be worthy of investigation.

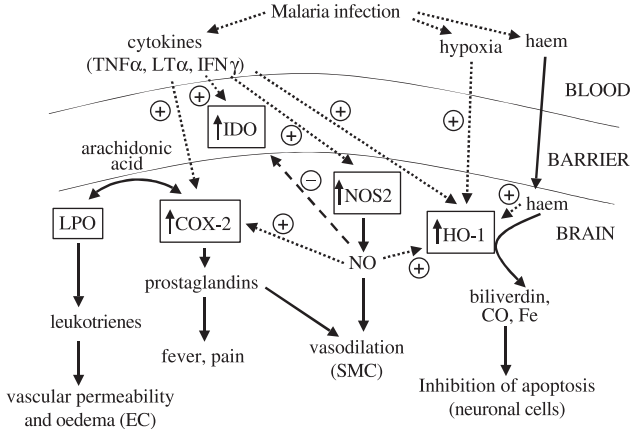

Fig. 5. Schematic diagram showing induction and some potential interactions and effects of haem enzyme pathways during cerebral malaria. The dotted arrows show the induction of protein expression or of physiological situations (e.g. hypoxia or production of haem from haemolysis). The bold arrows relate to the reactions catalysed by the enzymes and the physiological effects of their products. The dashed arrow represents the effect of a molecule on the activity of an enzyme. The plus and minus signs indicate a positive or negative effect on expression or activity. TNF, tumour necrosis factor; LTα, lymphotoxin-α; IFNγ, interferon-γ; IDO, indoleamine 2,3-dioxygenase; NOS2, inducible nitric oxide synthase; COX-2, cyclooxygenase-2; HO-1, haem oxygenase-1; LPO, lipoxygenase; EC, endothelial cell; SMC, vascular smooth muscle cell.

The role played by NO in CM is controversial (Clark et al., 1991; Lopansri et al., 2003) but overall the weight of the evidence gathered in human and mouse malaria points towards a possible protective action (Senaldi et al., 1992; Asensio et al., 1993; Kremsner et al., 1993; Stevenson et al., 1995; Anstey et al., 1996; Taylor et al., 1998; Favre et al., 1999; Sanni, 2001). The outcomes of human genetic studies of NOS2 polymorphisms and CM susceptibility do not allow clear-cut conclusions to be drawn (Burgner et al., 1998, 2003; Levesque et al., 1999; Mazier et al., 2000; Kun et al., 2001; Hobbs et al., 2002; Clark et al., 2003). NOS2 protein is certainly expressed in the brains of adults and some children who die from CM, in several cell types including endothelial cells, neurons, astrocytes and microglia (Maneerat et al., 2000; Clark et al., 2003b). NO has been implicated in the causation of severe malarial anaemia (Gyan et al., 2002).

The nature of any protection against CM afforded by NO/NOS2 is a matter for conjecture. NO inhibits the adherence to endothelial cells of PRBC containing *P. falciparum* (Serirom et al., 2003), though the magnitude of the effect is quite small, which would tend to lessen the focal reaction in the CNS. Another relevant possibility is that NO is a vasodilator, which potentially would be beneficial in conditions of restricted blood flow.

6. Summary and conclusions

Hopes for an end to the enormous disease problem posed by malaria currently revolve around the development of an effective vaccine and/or the introduction and implementation of cheap and effective anti-malarial drugs that do not induce parasite resistance. Work on the pathogenesis of malaria and its relevance to future treatment strategies has not been given due prominence in the past, particularly by major funding agencies. Two new strategies that may be highly effective in reducing morbidity and mortality associated with malaria are the development of 'anti-disease' vaccines (Schofield, 2002; Schofield et al., 2002; Good et al., 2005) and the identification of new drug targets in the host that can reduce life-threatening complications of the disease. Only by identifying the key targets of such strategies through more research on the pathogenesis of malaria can these prospects be realised.

Table 1
Summary of some mechanisms discussed in this article

Potential pathogenic factor	Associated mediators	Evidence in murine model of cerebral malaria	Evidence in human cerebral malaria
Increased blood–brain barrier permeability to protein		Thumwood et al. (1988), Chan-Ling et al. (1992) and Neill et al. (1993)	Brown et al. (1999a)
	Interferon-γ, lymphotoxin-α	Grau et al., 1989a,b, Jennings et al. (1997), Sanni et al. (1998), Amani et al. (2000) and Engwerda et al. (2002)	Rhodes-Feuillette et al. (1985), Chizzolini et al. (1990), Mshana et al. (1991), Wenisch et al. (1995) and Ho et al. (1995)
	Fas, FasL	Potter et al. (1999, 2006b)	
	Perforin	Potter et al. (1999, 2006a) and Nitcheu et al. (2003)	
	$CD8^+$T lymphocytes	Yanez et al. (1996), Hermsen et al. (1997), Belnoue et al. (2002) amd Potter et al. (2006a)	
	$CD4^+$T lymphocytes	Grau et al. (1986), Yanez et al. (1996) and Hermsen et al. (1997)	
Brain metabolic perturbations		Sanni et al. (2001), Rae et al. (2004) and Penet et al. (2005)	White et al. (1985), Warrell et al. (1988), Molyneux et al. (1989) and Medana et al. (2002b)
Kynurenine pathway activation		Sanni et al. (1998), Hansen et al. (2004) and Clark et al. (2005)	Dobbie et al. (2000) and Medana et al. (2002b, 2003)
Protective role of haem enzymes	Haem oxygenase-1		Schluesener et al. (2001)
	Cyclooxygenase-2	Ball et al. (2004)	Deininger et al. (2000) and Perkins et al. (2001)
	Nitric oxide synthase	Senaldi et al. (1992), Kremsner et al. (1993) and Favre et al. (1999)	Anstey et al. (1996), Boutlis et al. (2003), Serirom et al. (2003) and Lopansri et al. (2003)

In this article, we have emphasised a number of promising areas for exploration that have the possibility of identifying new therapies (Table 1). One such area is changes to the BBB that occur in human and murine CM, shown in the mouse to be through an immunopathological reaction involving $CD8^+$T lymphocytes (Belnoue et al., 2002; Nitcheu et al., 2003). Another is to identify the mechanisms that lead to the increased production of lactate in the CNS, which is a well-established indicator of a poor prognosis in human and experimental CM (White et al., 1985; Warrell et al., 1988; Molyneux et al., 1989). The issue of whether vascular obstruction or an immunopathological process involving cytokines is responsible for these changes has not been resolved as yet.

Evidence in mouse models, and to a lesser extent thus far in the human disease, has implicated the kynurenine pathway of tryptophan metabolism in the pathogenesis of CM (Sanni et al., 1998; Medana et al., 2002a,b,, 2003; Clark et al., 2005). Given the involvement of this pathway in disease complications such as AIDS dementia, pharmaceutical company interest in developing drugs that manipulate this pathway is current and real.

Finally, it seems that the host mounts a series of tissue protective responses to malaria infection that presumably are overwhelmed in severe malaria, including CM. Current indications are that some haem enzymes are key components of this host tissue protective response. Boosting host defences is a potential strategy for stabilising the progression of severe malaria until anti-malarial therapy, e.g. with artemisinin derivatives, can eliminate the parasite.

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