Iron is central to mammalian biochemistry and physiology. Its role extends from the haemoglobin molecule with its haem iron groups responsible for transporting oxygen, to the iron sulphur clusters found in mitochondrial respiratory chain enzymes that provide energy for cellular maintenance and metabolism (Crichton et al., 2002). Much has been learned about the peripheral changes that occur following altered body iron status either in deficiency, for example anaemia, or overload, such as haemochromatosis, but we are only now beginning to understand the regulation of iron in the nervous system. The brain is uniquely susceptible to perturbations in iron metabolism due to the high demand for energy to support neuronal activity (Morris et al., 1992a; Kann et al., 2011); and the relative absence of neuronal cell division leaves neurons open to attack by iron-mediated free radicals. Iron is also required for monoamine metabolism since tryptophan and tyrosine hydroxylase, and monoamine oxidase require iron as a cofactor; this places iron centrally within neurotransmitter systems needed for cognition, attention and motivation (Youdim and Yehuda, 2000). Iron shows complex mechanisms of uptake and distribution in the brain with access from the periphery relying on expression of the iron transport protein transferrin and its receptor at the blood–brain barrier (Taylor et al., 1991; Morris et al., 1992d). At the blood–brain barrier, iron is removed from transferrin, which recycles back to the periphery; iron is then transferred to the abluminal side of the barrier where astrocytes facilitate its further transport (Crowe and Morgan, 1992; Moos et al., 2006, 2007). In the adult brain, iron uptake is mainly into neurons where it supports neuronal oxidative metabolism. Transferrin receptors are expressed on neuronal cell bodies and transferrin is synthesized within the CNS (Mash et al., 1990; Taylor et al., 1991; Morris et al., 1992d; Gocht et al., 1993; Moos et al., 2007; Rouault et al., 2009). Iron uptake may be independent of transferrin and via the divalent metal transporter (DMT1) (Moos and Morgan, 2004; Moos et al., 2007). Thereafter, iron redistributes in the brain to its final destination within oligodendrocytes, microglia and astrocytes, being predominantly found in the basal ganglia; in fact the globus pallidus and substantia nigra pars reticulata can contain as much iron as the liver (Hallgren and Sourander, 1958; Morris et al., 1992c). How iron distributes within the brain between neurons and glia is poorly understood, but may involve mitochondrial catabolism and transfer to the intracellular iron storage protein ferritin, which is then exported from cells through ferritin receptor-mediated transport into glia (Morris et al., 1992b; Hulet et al., 1999; Todorich et al., 2008), or by ferroportin-mediated iron export from neurons (Donovan et al., 2005; Moos et al., 2007; Boserup et al., 2011). The transfer of iron into the brain appears to be essentially a one-way traffic (Taylor et al., 1991; Morris et al., 1992d). Although individuals with haemochromatosis show vascular and pituitary siderosis, there is no marked increase of iron in the brain parenchyma (Strassmann, 1945; Cammermyer, 1947) indicating tight regulation of iron ingress at the blood–brain barrier with steady accumulation occurring within the CNS throughout life (Hallgren and Sourander, 1958). Papers in this issue of Brain further demonstrate the effects of excess brain iron [the ‘lethal hard steel’ (Ahl, 2007)] and, conversely, the potential for iron deficiency to affect function of the nervous system (Rouault and Cooperman, 2006).

Krueer and colleagues (page 947) describe the neuropathology of one form of neuronal brain iron accumulation, pantothenate kinase-associated neurodegeneration, in a cohort of patients characterized at the molecular level. The cases studied all had homozygous or compound heterozygous mutations in the PANK2 gene with a presentation in infancy and early childhood—failure to reach developmental milestones, progressive dystonia and in many cases pigmentary retinopathy—that is typical for this disorder. T2 and T2* weighted MRI showed a hypointense region in the globus pallidus with central hyperintensity, the ‘eye of the tiger’ sign common to neuronal brain iron accumulation (Gregory and Hayflick, 2011), due to accumulation of high levels of iron. Pathologically, all of the cases showed the presence of neuroaxonal spheroids, associated with marked ubiquitin accumulation. As with all stimulating research, the study suggests questions for which there are at present, no answers. For example, what is the nature of the abnormal protein associated with this ubiquitin accumulation in spheroids? Given the types of mutation in PANK2 found in pantothenate kinase-associated neurodegeneration, it would be reasonable to assume that the spheroids derive from abnormally folded or processed PANK2...
protein although, since iron is known to stimulate free radical production, damage to neurofilament proteins or other major axonal proteins may play a role. Accumulation of tau in some cases may indicate that this is indeed occurring. Several issues need further thought: how the abnormally folded proteins found in pantotenate kinase associated neurodegeneration lead to axonal damage; how they contribute to iron accumulation in the basal ganglia; and, given that the abnormal iron observed in pantotenate kinase-associated neurodegeneration is associated with marked ubiquitin deposition, the surprising absence of marked α-synuclein deposition. There is a longstanding literature surrounding abnormalities of iron metabolism and neurodegeneration particularly for Parkinson’s disease (Koeppen, 1995). Synuclein-rich Lewy bodies are a virtual sine qua non for Parkinson’s disease and frequent reports of elevated iron in both the substantia nigra and elsewhere carry the tacit implication that iron may contribute or even cause α-synuclein deposition. However, in pantotenate kinase-associated neurodegeneration, as with other forms of neuronal brain iron accumulation such as neuroferritinopathy (Curtis et al., 2001), α-synuclein accumulation does not appear to be a significant feature, even in the presence of massive iron accumulation. One possibility is that iron is compartmentalized away from those neurons that are susceptible to Lewy body formation, in the form of neuronal brain iron accumulated in the globus pallidus and substantia nigra reticulata; or that iron only plays a role in the later stages of Parkinson’s disease as amplifier of a process that is already established. Finally, there is the issue of heterogeneity within pantotenate kinase-associated neurodegeneration, since the index case reported by Kruer et al. (2011) showed a delayed onset of symptoms and, compared with ‘typical’ earlier onset cases, slightly less-developed neuropathological changes. It is not yet certain that presence of the PANK2 c.370A>G mutation leads to a milder biochemical abnormality than is seen with the more common c.1231G>A mutation. Nor is the molecular mechanism whereby these mutations lead to iron accumulation and neurodegeneration established; but, as with many causes of neuronal brain iron accumulation, heterogeneity of clinical symptoms is a feature with atypical cases being common (Gregory and Hayflick, 2011). PLA2G6-associated neurodegeneration (PLAN) is a form of neuronal brain iron accumulation typically present as an infantile neuroaxonal dystrophy and showing iron accumulation but onset and clinical features that are markedly heterogeneous; in particular, late-onset manifests in some cases as dystonia parkinsonism (Khateeb et al., 2006; Morgan et al., 2006; Kurian et al., 2008; Paiser-Ruiz et al., 2009; Tonelli et al., 2010; Yoshino et al., 2010). Similarly, FA2H mutations are found in neuronal brain iron accumulation (Kruer et al., 2010) but heterogeneity of presentation is an issue also in this context (Edvardson et al., 2008). Carefully conducted studies of the type reported by Kruer et al. (2011) will provide a better understanding of neuronal brain iron accumulation, its pathology, molecular genetics and aetiology.

Iron deficiency anaemia, a major health burden recognized by the World Health Organization and affecting up to two billion people worldwide, is a treatable cause of nutrient deficiency (World Health Organization, 2001). Iron deficiency makes a significant impact on cognitive function with infants, children and adults showing memory impairment and reduced attention, but compared with the treatment of physical fatigue and anaemia, less consideration has been given to these neurological effects (Collard, 2009; Falkingham et al., 2010). Connor and colleagues (2011; page 959) report changes in the brain iron transfer system in the context of Restless Legs Syndrome, where altered iron homeostasis has previously been implicated (Trenkwalder and Paulus, 2010). Restless Legs Syndrome affects perhaps 5% of adults at any one time and has been shown to have a strong genetic aetiology (Stefansson et al., 2007; Winkelmann et al., 2007; Kemlinski et al., 2009; Trenkwalder et al., 2009; Vilarino-Guell et al., 2009), with clinical treatment centred mainly around the use of low-dose dopaminergic agents (Trenkwalder and Paulus, 2010). Some but not all studies implicate peripheral iron deficiency in Restless Legs Syndrome (Trenkwalder and Paulus, 2010). Cerebrospinal fluid concentrations of proteins involved in iron homeostasis are known to be altered in Restless Legs Syndrome suggesting that, despite adequate peripheral availability, there may be central iron deficiency (Earley et al., 2000; Mizuno et al., 2005; Clardy et al., 2006). Abnormalities in several proteins crucial to iron transport and metabolism at the blood–brain barrier and choroid plexus are seen in Restless Legs Syndrome, showing the potential for iron regulatory mechanisms to occur at this site (Connor, 2011). The blood–brain barrier is known to regulate iron entry into the brain (Taylor et al., 1991) and in the current study the potential for the iron regulatory protein IRP1 to play a role in this transport is indicated by the finding of decreased IRP1 activity in the blood–brain barrier in patients with Restless Legs Syndrome (Connor, 2011). This correlates with the finding of decreased transferrin receptor expression and, in turn, reduced blood–brain barrier transferrin, consistent with what is known about the physiology of iron entry to the CNS (Taylor and Morgan, 1991; Morris et al., 1992d). The decreased level of IRP1 in Restless Legs Syndrome would perhaps be expected when accompanied by decreased brain iron, though intuitively this might lead to increased transferrin receptor expression. Perhaps, decreased IRP1 binding to the 3′-UTR of transferrin receptor mRNA in Restless Legs Syndrome leads to enhanced mRNA degradation and decreased transferrin receptor protein along with decreased H-ferritin. But this leaves unanswered the reasons for decreased IRP1 in Restless Legs Syndrome and whether this involves enhanced degradation of IRP1 through proteins such as FBXL5, or imbalance elsewhere in iron regulation at the blood–brain barrier (Salahudeen et al., 2009; Vashisth et al., 2009). In a model of blood–brain barrier function, a second iron regulatory protein, IRP2, regulates ingress of iron and also manganese by increasing transferrin receptor and reducing ferritin protein expression (Li et al., 2005). IRP2 is also a candidate to regulate iron entry into the brain, since IRP2 regulates iron levels in states of altered iron delivery, while IRP1 regulates basal cellular iron (Meyron-Holtz et al., 2004). IRP2 deficiency also has major effects on brain iron, since mice lacking IRP2 show elevated brain iron and neurodegeneration providing a model of neuronal brain iron accumulation (LaVaque et al., 2001). The roles of genes involved in Restless Legs Syndrome such as MEIS1, BTBD9 and MAP2K5; how these affect brain iron homeostasis; and why central iron deficiency leads to the specific clinical symptoms observed in Restless Legs Syndrome are key questions for future work.
With iron metabolism being central to brain function, and cellular levels of iron dictating neuronal metabolism, it is surprising that we still know relatively little about how iron enters the brain and is utilized and distributed thereafter (Rouault and Cooperman, 2006; Rouault et al., 2009). The papers in the current issue highlight that both iron excess and deficiency can profoundly impact on brain function with catastrophic results in the case of pantothenate kinase-associated neurodegeneration and more pervasive effects in the context of Restless Legs Syndrome—findings that leave many Virgilian questions requiring ‘immediate attention’ (Ahl, 2007).

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