It is important to emphasize that we are dealing with intellectually highly able students and that these findings may not generalize to average students. Moreover, these results are of course not generalizable to particular individuals. Finally, it should be noted that the boys' SAT–M scores had a larger variance than the girls'. This is obviously related to the fact that more mathematically talented boys than girls were found (*14*). Nonetheless, the environmental hypotheses outlined above attempt to explain mean differences, not differences in variability. Thus, even if one concludes that our findings result primarily from greater male variability, one must still explain why.

Our principal conclusion is that males dominate the highest ranges of mathematical reasoning ability before they enter adolescence. Reasons for this sex difference are unclear (*15*).

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L-Tryptophan: A Common Denominator of Biochemical and Neurological Events of Acute Hepatic Porphyria?

Abstract. *Hepatic porphyrias are disorders of heme synthesis characterized by genetically determined lesions of one of the key enzymes of heme synthesis. In carriers of such lesions, several factors (drugs, environmental chemicals, or diet) precipitate acute and often fatal attacks of neurologic dysfunction, which are promptly relieved by intravenous infusion of heme. However, the mechanism of such heme-induced amelioration remains elusive. To probe this mechanism, the biochemical events triggered by acute hepatic heme deficiency were examined in an animal model of chemically induced porphyria. Acute hepatic heme depletion in porphyric rats was found to impair hepatic tryptophan pyrrolase activity which, in turn, elevated tryptophan and 5-hydroxytryptamine turnover in the brain. These alterations in porphyric rats were dramatically reversed by parenteral heme administration. These findings suggest that increased tryptophan and 5-hydroxytryptamine in the nervous system may be responsible for the neurologic dysfunctions observed in humans with acute attacks of hepatic porphyria.*

The three hepatic porphyrias—acute intermittent porphyria, hereditary coproporphyria, and variegate porphyria—are genetically transmitted disorders, each of which exhibits a defined defect of one of the enzymes essential for the formation of heme (*1*). The resulting heme deficiency in the liver removes the end-product (heme) repression of δ-aminolevulinic acid synthetase (ALAS), the first and rate-limiting enzyme of heme synthesis, leading to excessive formation and accumulation of heme precursors proximal to the particular enzyme block (*1*). Accordingly, depending on the site of the enzymatic defect, one may observe a pattern of heme precursor excretion that is characteristic for each of the three conditions (*1*).

In porphyric individuals, several factors, including exposure to a variety of common drugs or changes in hormonal status, diet, or fasting precipitate acute and often life-threatening attacks of neuropsychiatric dysfunction (*1*). Intravenous infusion of heme relieves or aborts these neurological manifestations (*1, 2*). However, the mechanism of this beneficial effect of heme is unknown. It is unlikely that administered heme directly substitutes for heme-deprived processes in the nervous system, because there is no evidence that infused heme enters the brain (*3*). The heme precursors δ-aminolevulinic acid (ALA) and porphobilinogen (PBG), which increase in concentration in the plasma of patients with acute forms of the hepatic porphyrias, produce neurotoxic effects in vitro (*4*), but there is no convincing evidence that they elicit neurological dysfunction when infused in large amounts in humans or animals (*5*). Moreover, neither ALA nor PBG appear to cross the blood-brain barrier to a significant extent (*5, 6*). The concentrations of these precursors in the brain or cerebrospinal fluid of porphyric patients are substantially below those required for demonstrable neurotoxicity in vitro (*7*). We therefore explored an alternative mechanism that might explain the heme-reversible neuropsychiatric dysfunction of acute heme deficiency in hepatic porphyrias.

Heme deficiency in the liver has a variety of metabolic consequences, including reduction in the activity of tryptophan pyrrolase, a cytosolic hemoprotein closely regulated by the hepatic "free" heme pool (*8*). Because this hemoprotein is the rate-limiting enzyme in tryptophan degradation (*9*), reduction of its hepatic activity raises plasma tryptophan concentrations and thereby enhances tryptophan transport into the brain (*10*). Since tryptophan availability in the brain limits the synthesis of the neurotransmitter 5-hydroxytryptamine (5HT, serotonin) (*11*), increased tryptophan in the nervous system would be expected to enhance production of 5HT and its metabolite, 5-hydroxyindoleacetic acid (5HIAA).

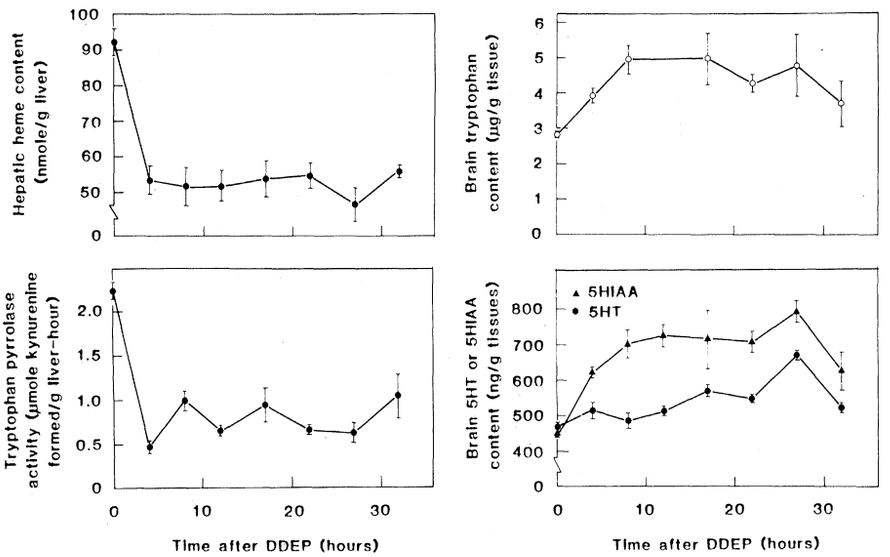

Fig. 1. Relation between hepatic heme content and tryptophan pyrrolase activity, and brain 5HT turnover in porphyric rats. Phenobarbital-treated animals received DDEP or no DDEP (controls) as described in the text. Hepatic heme content and tryptophan pyrrolase (holoenzyme) activity were determined as described (*23*). Whole brain tryptophan, 5HT, and 5HIAA were assayed as described (*24*). Values are means ± standard error of at least three animals killed at indicated times. Compared with corresponding values from untreated controls also killed at the designated times, all values from DDEP-treated animals were statistically significant (based on *t*-test at $P < 0.05$), with the exception of values for tryptophan pyrrolase activity and tryptophan at 32 hours and for 5HT at 12 hours, which were not statistically significant.

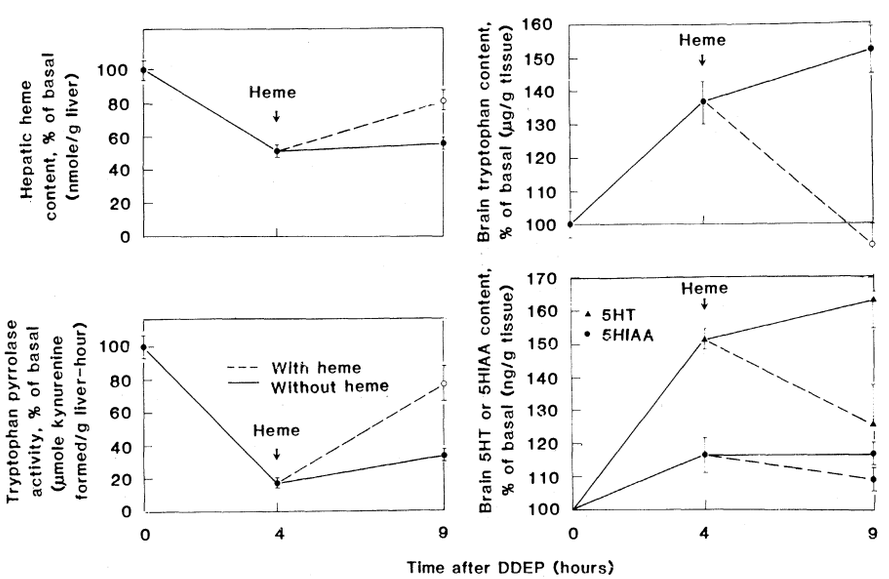

Fig. 2. Reversal of the reciprocal abnormalities of tryptophan metabolism in the liver and brain of porphyric rats after administration of exogenous heme. Phenobarbital-treated rats received DDEP for 4 hours, as described, at which time half the animals received hemin (11 mg/kg intraperitoneally, in two divided doses) and the other half received phosphate buffer, *p*H 7.4 (hemin controls). Hemin-treated and control animals were killed 5 hours later. Their total hepatic heme content and hepatic tryptophan pyrrolase activity, and brain tryptophan, 5HT, and 5HIAA were monitored as described in Fig. 1. Experimental values are reported as percentages of basal values in phenobarbital-treated controls (not given DDEP) and represent means ± standard error of at least three animals at each time point. The absolute values are indicated in Fig. 1.

Reduced plasma and brain tryptophan concentrations and brain 5HT turnover resulting from accelerated hepatic tryptophan breakdown have, in fact, been causally implicated in the pathogenesis of endogenous depression in humans (*12*). In contrast, elevated tryptophan resulting from potential compromise of hepatic tryptophan catabolism has been associated with human hepatic encephalopathy (*13*). In rats, hepatic injury or chronic portacaval shunt, each of which results in impaired hepatic tryptophan degradation and elevated circulating tryptophan, has been shown to produce structural alterations of brain astrocytes, oligodendroglia, and neurons, as well as degeneration of Purkinje cells and wasting of axons (*14*). Similar neurohistological alterations have been reported in victims of acute porphyric attacks (*15*), but whether elevated 5HT can be implicated in such pathogenic changes remains to be determined.

We found it intriguing that the pharmacological effects of 5HT in the central nervous system (where its function as an active neurotransmitter is well established) and in the gastrointestinal tract (where a similar role for 5HT is being increasingly recognized) resemble to a remarkable degree the neurological manifestations of acute porphyric attacks observed clinically (*1, 16*). Moreover, administration of tryptophan or 5-hydroxytryptophan to humans has been reported to result in severe abdominal pain, psychomotor disturbances, nausea, and dysuria—all of which are the principal symptoms of porphyria (*16*). Because of this striking resemblance and the fact that porphyric patients not only exhibit abnormal tryptophan metabolism (*17*) but also excrete relatively large amounts of 5-HIAA in the urine (*18*), we investigated whether the reduced hepatic tryptophan pyrrolase activity resulting from acute hepatic heme deficiency enhances tryptophan uptake and subsequent 5HT turnover in the brain.

Acute hepatic heme deficiency was induced in male Sprague-Dawley rats (200 to 250 g) by combined treatment with sodium phenobarbital (80 mg/kg, intraperitoneally, daily for 3 days) and a single intraperitoneal injection of

the porphyrinogen 3,5-dicarbethoxy-2,6-dimethyl-4-ethyl-1,4-dihydropyridine (DDEP, 125 mg/kg, in corn oil) for designated intervals before killing. All animals were killed 24 hours after the last injection of phenobarbital. Phenobarbital increases the demand for hepatic heme by inducing cytochrome P-450, a major hepatic hemoprotein. DDEP, however, is a potent depletor of hepatic heme by its combined property of selective destruction of hepatic cytochrome P-450 and subsequent alkylation of its heme to an *N*-ethylporphyrin, a potent inhibitor of ferrochelatase (*19*), the terminal enzyme in heme formation. This combined treatment was expected to result in acute heme deficiency, marked derepression of ALAS, and, consequently, exacerbated production of ALA and other heme precursors in the liver. Similar treatment with phenobarbital and the porphyrinogen DDC, the less potent 4-methyl analog of DDEP, in fact, has been shown to profoundly stimulate hepatic ALAS activity (*20*), resulting in accumulation of heme precursors and hence in a biochemically discernible porphyric state. Acute heme deficiency in this rat model was evidenced by the 50 percent decrease in hepatic heme content within 4 hours of DDEP administration (Fig. 1). Moreover, the 24-hour urinary uroporphyrin and coproporphyrin content in four animals was found to be elevated (6.65 ± 1.64 and 41.4 ± 11.7 μg per rat, respectively) compared to corresponding values (1.05 ± 0.16 and 4.75 ± 1.53 μg per rat, respectively) in control (phenobarbital-treated) animals ($N = 4$), thereby confirming that the rats were porphyric.

More notably, however, the decrease in hepatic heme content observed within 4 hours of DDEP administration was associated with a dramatic reduction of hepatic tryptophan pyrrolase activity (Fig. 1). This, in turn, was associated with increased brain tryptophan and consequently increased brain concentrations of 5HT and 5HIAA. Brain tryptophan, 5HT, and 5HIAA remained elevated throughout the period of observation, consistent with the lowering of hepatic heme and tryptophan pyrrolase activity which persisted over 32 hours of DDEP administration (Fig. 1). That acute hepatic heme deficiency was probably responsible for these reciprocal alterations in hepatic tryptophan degradation and brain 5HT-turnover in porphyric rats was shown by their reversal to near-normal levels within 5 hours of parenteral administration of heme (11 mg/kg) (Fig. 2). Similar findings were obtained in rats treated with phenobarbital and lead, an inhibitor of heme synthesis, indicating that these effects were not specific to the porphyric rat model used in our studies (*21*).

Collectively, these findings indicate that acute hepatic heme deficiency in porphyric animals results in significant elevation of tryptophan, 5HT, and 5HIAA in the brain. To our knowledge, this is the first demonstration of an alteration of a vital neurochemical within the central nervous system being elicited by acute hepatic heme deficiency and reversed by exogenous heme administration. Although enhanced 5HT and 5HIAA concentrations in the brain of chick embryos treated in ovo with DDC have been reported previously (*22*), the mechanism and the potential significance of this enhancement was not recognized. Together, these findings suggest that tryptophan may be the elusive common denominator of the biochemical abnormalities and the neurological manifestations associated with acute attacks of hepatic porphyria in humans.

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