Pellagra and Alcoholism: A Biochemical Perspective

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Abstract — Historical and clinical aspects of pellagra and its relationship to alcoholism are reviewed from a biochemical perspective. Pellagra is caused by deficiency of niacin (nicotinic acid) and/or its tryptophan (Trp) precursor and is compounded by B vitamin deficiencies. Existence on maize or sorghum diets and loss of or failure to isolate niacin from them led to pellagra incidence in India, South Africa, Southern Europe in the 18th century and the USA following the civil war. Pellagra is also induced by drugs inhibiting the conversion of Trp to niacin and by conditions of gastrointestinal dysfunction. Skin photosensitivity in pellagra may be due to decreased synthesis of the Trp metabolite picolinic acid —→ zinc deficiency —→ decreased skin levels of the histidine metabolite urocanic acid and possibly also increased levels of the haem precursor 5-aminolaevulinic acid (5-ALA) and photo-reactive porphyrins. Depression in pellagra may be due to a serotonin deficiency caused by decreased Trp availability to the brain. Anxiety and other neurological disturbances may be caused by 5-ALA and the Trp metabolite kynurenic acid. Pellagra symptoms are resolved by niacin, but aggravated mainly by vitamin B₆. Alcohol dependence can induce or aggravate pellagra by inducing malnutrition, gastrointestinal disturbances and B vitamin deficiencies, inhibiting the conversion of Trp to niacin and promoting the accumulation of 5-ALA and porphyrins. Alcoholic pellagra encephalopathy should be managed with niacin, other B vitamins and adequate protein nutrition. Future studies should explore the potential role of 5-ALA and also KA in the skin and neurological disturbances in pellagra.

INTRODUCTION

This article was prompted by the review in this journal (López et al., 2013) of historical, clinical and psychopathological aspects of pellagra encephalopathy in the context of alcoholism. Pellagra presents with some of or all the 3 D’s: dermatitis, diarrhoea and dementia (or more appropriately delirium, see Oldham and Ivkovic, 2012) and excellent reviews have been published on historical and clinical aspects (e.g. Rajakumar, 2000; World Health Organisation, 2000; Wan et al., 2011). I should like to add here a biochemical perspective, with particular emphasis on metabolism of the essential amino acid tryptophan (Trp), as it is the precursor of the pellagra-preventing factor nicotinic acid (niacin: also known as vitamin B₃). Known biochemical causes of pellagra and its symptoms are discussed and potential mechanisms are proposed.

HISTORICAL PERSPECTIVE OF NUTRITIONAL CAUSES OF PELLAGRA

Casal’s description of pellagra in 1735 was published in 1762. In 1771, Francesco Frapolli coined the name pellagra from the Italian pelle ogra (i.e. sharp or rough skin). In 1926, Goldberg showed that pellagra is caused by deficiency of a nutritional substance, which was identified as niacin by Elvehjem in 1937. The link between niacin and Trp was finally established in 1945 by Krehl (for references, see Wan et al., 2011).

As López et al. (2013) pointed out, introduction of maize from the Americas into Europe, wherein poverty and malnutrition were prevalent, was instrumental in the incidence of pellagra in Southern Europe during the 18th century. Arrival of pellagra in South Africa coincided with an outbreak of rinderpest in 1897 leading to the death of cattle, thus necessitating a change in the life style of the Bantu population from meat- to maize-eating, with little meat or milk intake (Bender, 1982). Pellagra in India has been associated with intake of maize and another staple, jowar (a variety of sorghum). In the Southern USA, pellagra became a serious medical problem following the American civil war, due to subsistence on a largely maize-based staple (Rajakumar, 2000). It was in the USA around the middle of the 20th century that most studies on the aetiology, prevention and cure of pellagra were undertaken.

Pellagra is thus a disease of malnutrition involving deficiency not only of the ‘B vitamin’ niacin, but also its Trp precursor, and is compounded by deficiencies of other nutrients, notably other B vitamins and possibly also zinc. Thus, niacin deficiency alone would not induce pellagra if adequate amounts of Trp are consumed in meat, dairy products, eggs or certain plant sources, and if metabolism of Trp to niacin along the hepatic kynurenine pathway is not impaired. Thus, Trp metabolism along this pathway is the major determinant of pellagra. Synthesis of 1 mg of niacin requires 60 mg of dietary Trp (Horwitt et al., 1956). There are wide individual variations in this 1:60 ratio, with factors such as pregnancy, hormonal differences and levels of Trp (protein) intake playing important roles (Bender, 1982). Daily niacin requirements of adults are ~15 mg. In the absence of niacin, a daily intake of ~1 g of Trp can meet these requirements. This necessitates intake of ~100 g of protein, as the Trp content of most proteins is ~1%, with some (richer) exceptions, notably milk, eggs, oats, sesame and sunflower seeds and soybeans. Truswell et al. (1968) reported average plasma Trp values in children with pellagra in South Africa of 12.7 μM (range: 4.9–23.5 μM), which rose upon recovery from protein calorie malnutrition to values of 19.6–36.2 μM. Adult controls exhibited values of 32–43 μM. Current adult normal plasma Trp values in the USA average 63 ± 20 μM (mean ± SD for n = 114) (Badawy et al., 2008).

Maize is a poor source of Trp. Its Trp content (~40 mg/g nitrogen) is at most one half of that (80–100 mg/g nitrogen) of cereals, such as barley, oatmeal, rice, rye and wheat. The Trp content of sorghum could be as little as 6.7–11.3 mg/g nitrogen, depending on the protein content of samples (Ravindran et al., 2011).
from urinary metabolite levels both under basal conditions, and, more importantly, after an oral Trp load (see below).

**Control of the pathway**

The rate-limiting enzyme of the pathway is the first, namely Trp 2,3-dioxygenase (TDO, formerly Trp pyrrolase). TDO activity is regulated by glucocorticoids and some other hormones, Trp, haem, and by feedback inhibition by the end product of the pathway NADPH. Among TDO important functions are control of hepatic haem biosynthesis and of Trp availability for cerebral serotonin synthesis (see the above reviews by Bender, 1982 and Badawy, 2002, 2005). TDO activity could also be inhibited by two intermediates of the pathway, 3-hydroxykynurenine and 3-hydroxyanthranilic acid, at near physiological concentrations (Wagner, 1964). Kynurenine hydroxylase, kynureninase and 3-hydroxyanthranilic acid oxidase are not rate-limiting, whereas picolinic acid carboxylase is, because this latter enzyme is at a cross point for synthesis of nicotinamide nucleotides and the tricarboxylic acid (Krebs) cycle intermediates, with the flux of Trp through the pathway favouring nucleotide synthesis. As the $K_m$ of kynurenine aminotransferase for its two substrates kynurenine and 3-hydroxykynurenine is much higher than those of kynurenine hydroxylase and kynureninase, the main metabolic route of kynurenine oxidation is via kynurenine hydroxylase followed by kynureninase, with little transamination (Bender, 1982). Transamination occurs to a significant degree only when there is an excess of the substrates caused by increased flux of Trp through the pathway (e.g. by Trp or kynurenine loading or TDO enhancement) and/or decreased activity of kynureninase. The increased transamination of kynurenine and 3-hydroxykynurenine following acute Trp loading (see, e.g. Michael et al., 1964; Price et al., 1965) results in the so-called functional vitamin B$_6$ deficiency, defined as decreased availability of the pyridoxal 5'-phosphate cofactor for enzymes requiring it beyond the aminotransferase and in other metabolic pathways. A major feature of this functional B$_6$ deficiency is increased urinary excretion of xanthurenic acid and, to a lesser extent, kynurenic acid. The active form of vitamin B$_2$ (flavinadene dinucleotide or FAD) is another cofactor required in the kynurenine hydroxylase reaction. Thus, deficiency of these two B vitamins can modulate production of intermediates at various steps of the pathway. Thiamine (vitamin B$_1$) deficiency does not influence the kynurenine pathway, but may contribute to pellagra symptoms by influencing haem metabolism (see below).

**Changes in the pathway associated with nutritional deficiencies in pellagra**

These are complex changes involving not only niacin deficiency, but also the associated general malnutrition, particularly that of protein and some B vitamins and a potential excessive leucine intake (Table 1).

**Protein deficiency**

As Trp is the niacin precursor, dietary protein deficiency can influence the kynurenine pathway at all levels, by decreasing Trp availability and hence its flux along the pathway (Fig. 1). Experimental protein deficiency decreases TDO activity (Satyanarayana and Rao, 1977), thus further

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**THE HEPATIC KYNURENINE PATHWAY OF TRYPTOPHAN DEGRADATION**

**Importance of the pathway**

A description of this pathway in some detail with special emphasis on nutritional aspects and the role of vitamin B deficiency can facilitate subsequent discussions of potential biochemical causes of pellagra and its symptoms. Figure 1 depicts the whole pathway, whereas Fig. 2 depicts reactions leading to niacin formation from quinolinic acid and subsequent metabolism. The hepatic kynurenine pathway is the major route of Trp degradation, accounting for $>95\%$ of Trp oxidation (Bender, 1982; Badawy, 2002, 2005). It produces important metabolites, including the pellagra-preventing factor niacin, the neuroactive compounds kynurenic (KA) and quinolinic (QA) acids, the important redox cofactors NAD$^+$ and NADPH$^+$ and their reduced forms NAD(P)H, and the zinc binding metabolite picolinic acid (PA). The liver is indispensable for niacin synthesis, because its kynurenine pathway contains all the required enzymes. Most studies of the human kynurenine pathway have been performed by measuring urinary, and occasionally plasma, metabolite levels, because, unlike Trp, which is poorly excreted in urine, plasma levels of kynurenine and subsequent metabolites are too small in comparison with those in urine. Thus, enzyme levels and disturbances in the human kynurenine pathway can be deduced

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**References**

and Bryden, 1997), but higher values have also been reported (see below). Maize, however, contains significant amounts of niacin, but combined with polysaccharides in the form of niacin, which cannot be hydrolysed by mammalian digestive enzymes (Bender, 1982). Most of the sorghum niacin ($~90\%$) is also similarly bound. Although peasants in Mexico and Central America have for millennia used maize as the main staple, and suffered from protein malnutrition as much as people in Southern Europe during the 18th century, the former have been generally free from pellagra (Carpenter, 1983). This is because the traditional process of preparing tortillas in Central America, known as ‘nixtamalización’, releases niacin by alkaline hydrolysis of niacin and is commonly described as the liming process. For example (see Rosadó et al., 2005), maize flour is first boiled (for 50 min) in a 1% aqueous calcium hydroxide solution before further processing. This chemical process was presumably unknown in Southern Europe or South Africa at the above times. In the USA, the process of ‘degemming’ in the preparation of cornmeal following development of the Beale degemerator in 1905 also reduced the niacin content, thus further contributing to pellagra incidence (Carpenter, 1981).

The maize- or sorghum-induced pellagra associated with malnutrition is compounded by the presence of relatively large amounts of the essential amino acid leucine (Leu). Whereas the average Trp content of maize and sorghum is 37.5 and 62.5 mg/g nitrogen, respectively, the corresponding Leu content is 794 and 700 mg/g nitrogen (FAO/WHO, 1973). With marginal nitrogen, respectively, the corresponding Leu content is 794 and 700 mg/g nitrogen (FAO/WHO, 1973). With marginal nitrogen, respectively, the corresponding Leu content is 794 and 700 mg/g nitrogen (FAO/WHO, 1973).

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**Figure 1**

- Depicts the whole pathway, whereas Fig. 2 depicts reactions leading to niacin formation from quinolinic acid and subsequent metabolism.

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**Figure 2**

- Depicts reactions leading to niacin formation from quinolinic acid and subsequent metabolism.
to the decreased flux, and those of picolinate carboxylase, nicotinamide N-methyltransferase and N-methylnicotinamide oxidase, but not those of kynurenine hydroxylase, kynurenine aminotransferase, kynureninase and quinolinate phosphoribosyltransferase (Hayakawa and Iwai, 1985; Shibata et al., 1988).
Table 1. Effects of nutritional deficiencies and excess leucine intake on enzymes of the hepatic kynurenine pathway of tryptophan metabolism

<table>
<thead>
<tr>
<th>Enzyme</th>
<th>Deficiency of:</th>
<th>Excess of: Leucine</th>
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<tbody>
<tr>
<td></td>
<td>Protein (Trp)</td>
<td>Niacin B₁ B₂ B₆</td>
</tr>
<tr>
<td>Tryptophan dioxygenase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Kynurenine aminotransferase</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Kynurenine hydroxylase</td>
<td>N</td>
<td>N</td>
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<tr>
<td>Kynureninase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>3-Hydroxyanthranilic oxidase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Picolinic carboxylase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Quinolinate phosphoribosyl transferase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Nicotinate phosphoribosyl transferase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Nicotinamide deaminase</td>
<td>N</td>
<td>N</td>
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<tr>
<td>NAD Synthetase</td>
<td>N</td>
<td>N</td>
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<tr>
<td>NADase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Nicotinamide phospho-ribosyltransferase</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>NAD kinase</td>
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<td>N</td>
</tr>
<tr>
<td>Nicotinamide N-methyltransferase</td>
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<td>N</td>
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<tr>
<td>N-Methylnicotinamide oxidase</td>
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<td>N</td>
</tr>
</tbody>
</table>

Symbols: ↓, inhibition; ↑, enhancement; N, normal when assayed directly; ?, not clearly established. Absence of symbols indicates assumption of normality and/or status not determined.
Niacin deficiency causes pellagra and impairs steps in the kynurenine pathway beyond niacin synthesis (Brown et al., 1958; Shibata et al., 1995). It inhibits the formation of the two major niacin metabolites N^6^-methyl nicotinamide and 1-methyl 2-pyridone 5-carboxamide, the urinary excretion of which is the standard test of niacin deficiency, and the synthesis of the important redox cofactors NAD^+ (P^+)H (Fig. 1), thereby undermining the activities of the hundreds of dehydrogenases, hydroxylases, oxidases and other enzymes involved in various vital biochemical processes, including energy production. Modulation of these important functions is instrumental in the development of pellagra symptoms, as it targets tissues with high cellular turnover (skin and gastrointestinal tract) and high energy requirements (brain), hence the 3 D’s. The above biochemical changes and the associated clinical perturbations can be reversed by dietary niacin supplementation. In pellagra, however, altered Trp metabolism via the kynurenine pathway also occurs, partly as a consequence of niacin deficiency decreasing NADPH and also by the associated deficiencies of Trp and some B vitamins. As stated above, TDO is regulated by a feedback inhibitory mechanism exerted by NADPH (Badawy, 2002, 2005 and references cited therein). With niacin deficiency, this feedback control is removed, which could enhance TDO activity. With TDO induction, urinary excretion of kynurenine metabolites is enhanced, particularly after a Trp load (Hankes et al., 1971), possibly through enhanced transamination leading to a functional vitamin B6 deficiency. Activities of enzymes of the kynurenine pathway are not altered in experimental niacin deficiency (Shibata et al., 1995). However, in pellagra patients, TDO enhancement is also accompanied by inhibition of activity of the NADPH-dependent kynurenine hydroxylase in vivo, evidenced by the low urinary excretion of 3-HK (Hankes et al., 1971).

Niacin supplementation also exerts effects of its own. Acutely, niacin does not affect rat liver TDO activity (Wagner, 1964) and the enhancement caused by an acute large dose is mediated by adrenal glucocorticoids. However, chronic nicotinamide administration causes a NADPH-mediated inhibition (Badawy and Evans, 1976). This end-product inhibition could explain the ‘sparing effect’ of niacin on Trp. Dietary Trp is more effective in increasing the synthesis of these pyridine dinucleotides than dietary niacin (Williams et al., 1950). Dietary niacin supplementation of pellagrin consuming a corn diet corrects the abnormal urinary excretion of kynurenine metabolites (Hankes et al., 1971).

Dietary Leucine

As stated above, the high levels of leucine (Leu) compound the effects of niacin deficiency associated with maize and sorghum intake. Leu and other branched-chain amino acids (BCAA) are metabolized by the pyridoxal 5’-phosphate-dependent enzyme BCAA aminotransferase to their corresponding keto acids, converting in the process 2-oxoglutarate to glutamate. In the vitamin B6 deficiency associated with pellagra, Leu transamination could be impaired and this may explain the observed (Bapurao and Krishnaswamy, 1978) decrease in disposal of plasma Leu following a Leu loading test, which is normalized and/or enhanced by B6 supplementation. Conversely, an excess of Leu could deplete pyridoxal 5’-phosphate and thus decrease activities of kynureninase and other B6-dependent enzymes. In the absence of niacin deficiency, the effects of Leu are on Trp metabolism and not on utilization of nicotinamide or niacin (Magboul and Bender, 1981). Excess dietary Leu enhances TDO and picolinate carboxylase, inhibits kynureninase and quinolinate phosphoribosyltransferase, but exerts no effect on 3-hydroxyanthranilic acid oxidase or nicotinate phosphoribosyltransferase (Bender, 1983; Bender and Magboul, 1984 and references cited in both). These effects explain the decreased synthesis of quinolinic acid and nicotinamide nucleotides when dietary niacin intake is marginal (Magboul and Bender, 1983) and the increased urinary excretion of kynurenine, 3-hydroxykynurenine and kynurenic and xanthurenic acids especially after a Trp load (see, e.g. Hankes et al., 1971). Excess dietary Leu has also been suggested to inhibit intestinal Trp absorption competitively (Sakakibara et al., 1982).

Vitamin B6

The relationships and interactions between pyridoxine and niacin deficiencies in relation to hepatic Trp metabolism are very important, but complex (Hankes et al., 1971; Bender, 1982; Shibata et al., 1995). As pyridoxal 5’-phosphate is the cofactor of kynurenine aminotransferase and kynureninase, pyridoxine deficiency inhibits activities of both enzymes (see, e.g. Shibata et al., 1995). An important feature of pyridoxine deficiency is increased urinary excretion of the transamination products xanthurenic acid and kynurenic acid (Charconnet-Harding et al., 1953). The increased excretion of xanthurenic acid could be explained by the kynureninase inhibition (Knox, 1953) and stimulation of kynurenine hydroxylase (Shibata et al., 1995) causing accumulation of 3-hydroxykynurenine. TDO enhancement may also play a role, though this is somewhat disputed (Kondo and Okada, 1985; Shibata et al., 1995). B6 deficiency does not alter activities of 3-hydroxyanthranilic acid oxidase, picolinate carboxylase, nicotinamide phosphoribosyltransferase, nicotinamide N-methyltransferase and N-methylnicotinamide oxidase (Shibata et al., 1995).

Dietary pyridoxine supplementation provides the pyridoxal 5’-phosphate cofactor of kynurenine aminotransferase and kynureninase, thereby reversing the effects of deficiency of this vitamin. Pyridoxine administration (10 mg/kg) to normal rats inhibits TDO activity over a 4 h period (Bender and Totoe, 1984), but not at later time intervals (Sardesai et al., 1986). This inhibition is likely to be mediated by pyridoxal 5’-phosphate, as it inhibits TDO in vitro (Sardesai et al., 1986).

Vitamin B1

Thiamine does not seem to play an apparent role in Trp metabolism via the kynurenine pathway and current evidence does not support a negative effect of its deficiency on Trp metabolism. Thus, TDO activity is either unaltered (Chiancone, 1964) or increased (Hauschildt, 1975; Shibata et al., 1997) in thiamine deficiency, with the conversion ratio of Trp to niacin rising by 7-fold (Shibata et al., 1997). The latter authors suggested that vitamin B1 can only have a minor involvement in the conversion of Trp to niacin.

Vitamin B2

Riboflavin deficiency can affect Trp metabolism along the kynurenine pathway. Thus, riboflavin-deficient rats...
excrete increased amounts of anthranilic and xanthurenic acids (Charconnet-Harding et al., 1953). The former effect is unrelated to Trp metabolism, whereas the xanthurenic acid elevation, which is reversible upon riboflavin supplementation, may involve an action on a phosphorylative, rather than an oxidative, step. In addition to increased urinary excretion of anthranilic acid, riboflavin deficiency in baboons (Verjee, 1975) increases that of kynurenic acid by 2-fold and decreases those of 3-hydroxykynurenine (10-fold), 3-hydroxyanthranilic acid (3-fold) and N-methyl nicotinamide (3-fold). This huge reduction in 3-hydroxykynurenine (and the simultaneous elevation of kynurenic acid) is due to inhibition of kynurenine hydroxylase as a result of decreased cofactor availability and decreased NAD+ (P+) synthesis (Bender, 1996). Impaired kynurenine hydroxylase in a 9-year old girl with pellagra with colitis is also associated with increased kynurenic acid (and kynurenine) and decreased xanthurenic acid excretion in urine (Clayton et al., 1991). Thus riboflavin deficiency may induce a niacin deficiency by inhibiting kynurenine hydroxylase and possibly also kynureninase.

OTHER CAUSES OF PELLAGRA

As well as from the above dietary deficiencies and high Leu intake, pellagra can be caused by drugs, conditions associated with gastrointestinal (GIT) disturbances, and alcohol dependence. Alcohol will be considered separately below.

Drugs

Drugs can induce pellagra by inhibiting metabolism of niacin or its Trp precursor. Examples include azathioprine, chloramphenicol, ethionamide, 5-fluorouracil, isoniazid, 6-mercaptopurine, pyrazinamide and many others (for references, see Wan et al., 2011). Niacin synthesis from Trp could be impaired by inhibition of protein (enzyme) synthesis at the transcriptional or translational level by the above antibiotics and immunosuppressant drugs, not only of the rate-limiting enzyme TDO, but also potentially other subsequent enzymes of the pathway. With isoniazid, kynureninase inhibition by inactivation of pyridoxal 5′-phosphate decreases the availability of precursors for niacin synthesis and the resulting pellagra can be treated with vitamin B6 supplements (see Bender, 1982). Oestrogens, which can cause secondary pellagra, may also undermine niacin formation by the same mechanism (Bender, 1982).

Conditions associated with gastrointestinal disturbances in pellagra

GIT disturbances of pellagra begin with dyspepsia, burning sensation in throat, constipation and diarrhoea, and progress to the more severe symptoms of abdominal pain and bleeding, nausea and diarrhoea with intestinal bleeding. These GIT abnormalities occur in niacin deficiency induced by conditions causing GIT dysfunction, e.g. the metabolic diseases of Hartnup and the carcinoid syndrome, anorexia nervosa, HIV infection and conditions interfering with niacin intake, absorption or processing. Protein and other nutrient deficiencies may be important determinants. Hartnup disease is associated with aminoaciduia (Baron et al. 1956) leading to decreased Trp availability to the liver for synthesis of niacin and the pellagra in this condition is treatable with exogenous niacin, but not Trp. Loss of Trp also limits cerebral serotonin synthesis, which may explain some of the associated neurological abnormalities (see below). In the carcinoid syndrome, most of available Trp is diverted to peripheral serotonin synthesis, limiting Trp availability to the liver for niacin formation (see, e.g. Swain et al. 1976). Conditions interfering with niacin intake, absorption or processing include chronic colitis, coeliac disease, Crohn’s disease, severe ulcerative colitis, gastroenterostomy, GIT tuberculosis, hepatic cirrhosis, jejuno-ileitis, regional ileitis, severe ulcerative colitis and subtotal gastrectomy (for references, see Wan et al., 2011). Impaired niacin availability is the common determinant and GIT symptoms are reversible by niacin supplementation with adequate nutrition.

CLINICAL FEATURES OF PELLAGRA

Although pellagra is commonly associated with the 3 D’s, nowadays not all patients present with all three conditions. GIT disturbances have been described above.

Skin features

The most striking feature of pellagra is skin photosensitivity. The classification and phenotypic characterization of the various forms of niacin deficiency photosensitivity have been reviewed and a number of theories have been advanced to explain the biological basis of the skin lesions (Wan et al., 2011). These are described and expanded in the following discussion (Table 2).

<table>
<thead>
<tr>
<th>Table 2. Potential mechanisms of the skin and neurological features of pellagra</th>
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<tbody>
<tr>
<td><strong>Mediator</strong></td>
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<tr>
<td>Skin features</td>
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<tr>
<td>Niacin deficiency</td>
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<tr>
<td>Uric acid deficiency</td>
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<tr>
<td>Zinc deficiency</td>
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<td>Picolinic acid deficiency</td>
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<td>Pyridoxine deficiency</td>
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<td>Kynurenic acid</td>
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<tr>
<td>5-Aminolaevulinate acid</td>
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<td>Neurological features</td>
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<tr>
<td>Serotonin deficiency</td>
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<tr>
<td>Kynurenic acid</td>
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<tr>
<td>5-Aminolaevulinate acid</td>
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</table>
Deficiency of NAD⁺(P⁺)

Deficiency of these cofactors may contribute to skin disturbances by two mechanisms: (i) impaired repair of UV damage to the epidermis; (ii) decreased energy transfer to rapidly turning over skin cells (for references, see Wan et al., 2011). It should be noted that vitamin B₆ deficiency will also impair the formation of nicotinamide nucleotides and it is of interest that the skin lesions in vitamin B₆ deficiency are similar to those of both pellagra and acrodermatitis enteropathica (Krieger, 1981) (see further below).

Urocanic acid

The decreased concentration of this histidine (His) metabolite in skin of pellagrins (National Institute of Nutrition, Hyderabad, 1968/9) could explain the skin lesions, as it is a major ultraviolet-absorbing compound in normal skin. His is metabolized to glutamate in a pathway that starts with hydrolysis of His to urocanic acid by the action of histidase. Vasantha (1970) reported that histidase activity and concentrations of His and urocanic acid are all decreased in skin of pellagrins, but are all elevated following niacin treatment. This is somewhat surprising, as a low histidase activity should be associated with a high, rather a low, [His]. Also, patients with the inherited metabolic disorder histidinaemia who exhibit lower skin levels of urocanic acid are all decreased in skin of pellagrins, but could involve disturbances in haem metabolism. His oxidation leading to decreased tissue concentrations of both His and its metabolite urocanic acid do not suffer from skin photosensitivity (Levy et al., 2001). Other factors must therefore be involved. One potential factor is zinc deficiency, possibly related to Trp metabolism, but also to general malnutrition.

Zinc deficiency

The potential role of Zn deficiency is suggested by the clinical similarities in the dermatitis of pellagra, the hereditary Zn deficiency condition acrodermatitis enteropathica, and nutritional Zn deficiency (Krieger, 1981). Zn deficiency is associated with increased His oxidation leading to decreased tissue concentrations of both His and its metabolite urocanic acid (Hsu and Rubenstein, 1981). However, the potential role of Zn deficiency in the skin lesions cannot be attributed to decreased urocanic acid for the reason mentioned above in relation to histidinaemia, but could involve disturbances in haem metabolism (see below) and impaired formation of the Trp metabolite picolinic acid (PA).

Picolinic acid

Intestinal absorption of Zn is achieved by a zinc-binding substrate derived from exocrine pancreatic secretion. Human, but not bovine, milk is rich in this substance and Evans and Johnson (1980) identified it as the Trp metabolite PA. As stated above, the flux of Trp along the kynurenine pathway (Fig. 1) favours the formation of nicotinamide nucleotides via the non-enzymatic cyclisation of acroleyl aminofumarate to quinolinic acid. Only when the flux of metabolites is so great that the enzyme competing with the non-enzymatic cyclisation of aminomuconic semialdehyde is saturated with its substrate can significant amounts of PA be formed. As the opposite is true in pellagra, PA formation will be impaired leading to decreased absorption of Zn and a consequent decrease in the histidine metabolite urocanic acid as a result of accelerated histidine oxidation.

Kynurenic acid

The increased formation of this Trp metabolite in pellagra (see above) may also contribute to the skin disturbances. KA can induce a phototoxic skin reaction following exposure to long-wave UV radiation ranging from 350 to 380 nm (Hendricks, 1991). However, other than the ability of niacin supplementation to normalize KA levels, the possible role of KA in the skin abnormalities has not been studied.

Porphyrin metabolic disturbances

Another potential contributor to pellagra-induced skin photosensitivity is altered porphyrin metabolism, proposed by Gillman et al. (1945) based on the observation of porphyrin-related fluorescence in livers of pellagrins. Zinc deficiency may have a potential role here, as it could inhibit activity of the Zn-dependent enzyme 5-aminolaevulinic acid dehydratase (ALAD) (Gibbs et al., 1985). This results in accumulation of the ALAD substrate 5-aminolaevulinic acid (5-ALA) and altered formation of porphyrins. Porphyrins fluoresce. In porphyria cutanea tarda, porphyrins are irradiated by UV light and it is thought that the release of trapped energy following skin exposure to light underlies the photosensitivity. 5-ALA is already used in skin conditions (Tzogani et al., 2013) as a source of photo-activated porphyrins. 5-ALA levels could also be increased if its transamination product 4,5-dioxovaleric acid is elevated. This could result from increased production of glyoxylate caused by thiamine deficiency (Hauschmidt, 1975). Liang (1962) demonstrated the increase in glyoxylate in experimental thiamine deficiency and attributed it to increased glycine from tissue breakdown. Truswell et al. (1968) reported a doubling of plasma glycine levels in pellagra. 5-ALA is a potential candidate worthy of investigation in pellagra, as its skin levels could be increased by deficiency of both Zn and thiamine. As will be discussed below, 5-ALA accumulation could also play an important role in the neurological disturbances of pellagra.

Neurological features

Early symptoms of pellagra are mainly those of depression and anxiety. More severe neurological disturbances occur generally in relatively advanced pellagra and can range from mild delusions and confusion to psychosis (Bender, 1982).

Depression

Depression may be due to impaired cerebral serotonin synthesis caused by the decrease in availability of its Trp precursor secondarily to protein malnutrition. The rate-limiting enzyme of serotonin synthesis, Trp hydroxylase, is unsaturated with its Trp substrate, hence the importance of brain [Trp] (see Badawy, 2002). As the brain cannot synthesize Trp, it has to rely on its availability in the circulation. Trp enters the brain in competition with a number of competing amino acids (CAA), notably the branched-chain amino acids (BCAA) Leu, Ile and Val and the aromatic amino acids Phe and Tyr. Accordingly, Trp availability to the brain is expressed as the ratio of plasma [Trp]/[CAA]. As stated above, plasma [Trp] is decreased in pellagra (Truswell et al., 1968). Calculation of the [Trp]/[CAA] ratio (μM/μM) from the data by these authors, but including only 4 CAA (as no data on Phe were provided) shows
that the ratio was indeed very low in the eight pellagra children before therapy (0.034), but rose to 0.052 after recovery, with the control ratio being 0.080. As far as I could ascertain, no similar data have been reported in pellagra patients, except those with alcoholism (see below).

Another potential contributor to serotonin deficiency in pellagra is a possible impaired decarboxylation of the immediate serotonin precursor 5-hydroxytryptophan by the pyridoxal 5′-phosphate-dependent aromatic L-amino acid decarboxylase (ALAAD), whose activity is impaired in (functional) vitamin B6 deficiency. Excess dietary leucine can also contribute to the serotonin deficiency by Leu competing with Trp for cerebral uptake and possibly also by stimulating liver TDO activity (see above).

**Anxiety**

Decreased serotonergic activity may also play a role in anxiety (Meltzer and Lowy, 1987) and it is well-established that serotonin-specific reuptake inhibitor (SSRI) antidepressants induce anxiety soon after the start of therapy (Baldwin et al., 2005), possibly by decreasing serotonin turnover and/or modulating neurosteroids. Increased serotonin synthesis and turnover caused by deletion of the mouse TDO gene are associated with decreased anxiety in two behavioural models (Kanai et al., 2009). Thus, anxiety in pellagra could arise, at least in part, from the associated serotonin deficiency.

The role of the major inhibitory neurotransmitter γ-amino butyric acid (GABA) in anxiety disorders is well established (Möhler, 2012). The haem precursor 5-ALA may play a role in the pellagra anxiety as it is a powerful inhibitor of GABA release (see further below).

**Other neurological disturbances**

Biochemical correlates of the more advanced neurological disturbances are less clearly defined. Potential mediators are increased kynurenic acid/quinolinic acid ([KA]/[QA]) ratio and increased production of the porphyrin and haem precursor 5-ALA. KA and QA modulate the NMDA (N-methyl-D-aspartate) type of receptors of the excitatory amino acid glutamate in opposite directions; KA being an antagonist and QA an agonist (Stone, 1993), and the above ratio determines the overall level of neuronal excitability. The increase in the above ratio results in glutamatergic hypoactivity, which is now considered a major feature of schizophrenia, with KA playing a central role (see Badawy, 2013). Although there are similarities between the advanced neurological features of pellagra and those of schizophrenia, it is possible that glutamatergic hypoactivity is common to both conditions, with dopaminergic overactivity being limited to the majority of patients with schizophrenia. Unlike that of kynurenine, KA entry into the brain is very limited (Fukui et al., 1991). Accordingly, potential increase in brain [KA] in pellagra is likely to result from increased kynurenine uptake and its subsequent transamination, as levels of this KA precursor are increased in pellagrins (Hankes et al., 1971).

A potential mediator of the severe neurological features of pellagra is the haem precursor 5-ALA. The haem-biosynthetic pathway is controlled by the first enzyme, 5-aminolaevulinic acid synthase (5-ALAS), a mitochondrial pyridoxyl 5′-phosphate-dependent enzyme that catalyses the condensation of succinyl-Co-A and glycine to form 5-ALA. Feedback control of the pathway involves repression of 5-ALAS by a small pool of ‘free’, ‘unassigned’ or ‘readily exchangeable’ haem in the hepatic cytosol, the size of which is ~10⁻⁷ M, and which is utilized by TDO (Badawy, 1979 and references cited therein). Induction of 5-ALAS therefore occurs when the negative feedback control is undermined, e.g. by increased utilization of haem (by TDO) or inhibition of its synthesis at steps beyond the first. In pellagra, this pathway could be disturbed in a number of ways: (i) the zinc deficiency can inhibit the second enzyme of the pathway, the Zn-dependent 5-ALA dehydratase (5-ALAD), thus leading to accumulation of 5-ALA and some porphyrins; (ii) the associated thiamine deficiency can further contribute, via glyoxylate, to the 5-ALA elevation, as discussed above and also by inhibition of 5-ALA by the intermediate 5-hydroxy-4-oxovaleric acid (Hauschmidt, 1975); (iii) the associated pyridoxine deficiency can inhibit 5-ALAS. The balance between these three factors will therefore determine the final level of 5-ALA. 5-ALA is neurotoxic and appears to mediate the neurological disturbances in acute porphyric attacks via a number of mechanisms including direct cytotoxicity (for review, see Pischik and Kauppinen, 2009). 5-ALA is a potent presynaptic GABA agonist (Brennan and Cantrill, 1979) associated with depersonalization, dysphoria and visual hallucinations in porphyria (Pepplinkuizen et al., 1980). A 1 μM concentration of 5-ALA inhibits presynaptic GABA release by 50% (Brennan and Cantrill, 1979) and its CSF level is elevated during an acute porphyric attack (Sweeney et al., 1970) to values well above that causing this level of inhibition (see also Pepplinkuizen et al., 1980). Thus 5-ALA is a strong candidate for mediating the psychotic and confusional states (Meldrum, 1982) in conditions such as pellagra. 5-ALA has not been studied in pellagra and it is therefore unclear if its concentration in blood is sufficiently large to produce cerebral levels capable of inhibiting GABA release. In the study by Sweeney et al. (1970) CSF [5-ALA] during porphyric attack (21 μM) was 11.47% of that in plasma (183 μM). Although brain levels have not been determined, they could be generally assumed to be ~10-fold higher than those in CSF, as is the case in Trp.

**AGGRAVATION OF PELLAGRA SYMPTOMS BY B VITAMINS**

López et al. (2013) and others (Serdaru et al., 1988; Teare et al., 1993; Pittsava et al., 2004) reported aggravation of the neurological features of pellagra after intake of B vitamins other than niacin, namely B1, B2 and B6, and B12. Potential mechanisms of this aggravation have been proposed, including anatomical disturbances and prostaglandin involvement (see López et al., 2013). In the light of earlier discussions of the effects of deficiencies of these vitamins on Trp metabolism, the following hypotheses are proposed. (i) Involvement of supplemental thiamine and riboflavin can be reasonably excluded, as their deficiency either increases 5-ALA (thiamine) or inhibits kynurenine hydroxylase and possibly also kynureninase activity (riboflavin). (ii) However, it is also possible that thiamine supplementation may contribute to pellagra encephalopathy by increasing the demand for NAD nucleotides (for references, see Serdaru et al., 1988). (iii) In the above studies with various combinations of B vitamins (excluding niacin), the common denominator was B6. This B vitamin is therefore the most likely major cause of the aggravation. As discussed earlier, exogenous
pyridoxine supplementation can exert effects on haem and Trp metabolism along the kynurenine pathway at several steps, all of which could further aggravate the neurological features of niacin deficiency. These effects are: (i) activation of 5-ALAS leading to increased formation of 5-ALA and its subsequent accumulation because of a Zn deficiency-induced inhibition of 5-ALA activity; (ii) as 5-ALA is a potent GABA agonist, it can induce an acute psychotic syndrome if present in excess (Meldrum, 1982); (iii) TDO inhibition by pyridoxal 5'-phosphate can further decrease niacin precursor availability; (iv) activation of kynurenine aminotransferase could increase the NMDA antagonist kynurenic acid, elevation of which in cerebrospinal fluid is a core feature of the kynurenic acid theory of schizophrenia (Linderholm et al., 2012). However, as pellagra involves multiple vitamin B deficiencies, supplements must contain niacin and consideration could be given to including a smaller, rather than a large, pyridoxine dose. In any case, vitamin supplementation should always be accompanied by adequate protein (Trp) intake.

**ALCOHOL-INDUCED PELLagra**

While pellagra is still widespread in certain parts of the world where malnutrition is predominant, it is also encountered occasionally in more developed countries, such as Brazil (Bruno et al., 2013), Denmark (Lorentzen et al., 2000), France (Serdaru et al., 1988), Greece (Pitsavas et al., 2004), Japan (Ishii and Nishihara, 1981), Spain (López et al. (2013), the Netherlands (Pasmans et al., 1998) and the USA (Oldham and Ivkovic, 2012). Chronic alcoholism is a common feature in all cases. The three major features of alcoholic pellagra are fluctuating confusional states and/or clouding of consciousness, oppositional hypertonus and startle myoclonus (Serdaru et al., 1988) and although alcoholic pellagra encephalopathy can be distinguished from other encephalopathies by clinical, biochemical and pathological means, they often occur simultaneously. Accordingly, multiple B vitamin therapy including niacin is advisable (Serdaru et al., 1988; Cook et al., 1998).

Alcohol can induce pellagra through the associated malnutrition decreasing availability and/or impairing absorption of niacin, its precursors and other vitamins and nutrients. Additionally, alcohol may accentuate the effects of the nutritional deficiencies by exerting effects of its own. Alcohol-specific effects may include metabolic consequences of alcohol metabolism, impaired conversion of Trp to niacin, induction of Zn deficiency, perturbation of haem biosynthesis and disturbances of glutamate and GABA neuronal activity. The following is a discussion of these potential effects (Table 3) and their possible impacts on the clinical features of pellagra.

**Table 3. Mechanisms in alcoholic pellagra**

| Nutritional | (1) Protein, vitamin B and zinc deficiencies  
| Biological | (2) Impaired absorption and processing of nutrients  
| Biological | (1) Inhibition of liver tryptophan 2,3-dioxygenase and of subsequent formation of niacin precursors  
| Biological | (2) Inactivation of pyridoxal 5'-phosphate by acetaldehyde  
| Biological | (3) Decreased NAD+ cofactors  
| Biological | (4) Accumulation of the porphyrin precursor 5-aminolaevulinic acid  
| Physiological | (1) Disturbances of glutamate and GABA neuronal activity  

**Alcohol metabolism and cofactor availability in pellagra**

Little information is available on alcohol metabolism in pellagra. Depletion in pellagra of the NAD+ cofactor of alcohol dehydrogenase (ADH) and of the NADPH cofactor of the microsomal ethanol-oxidizing system (MEOS) involving the cytochrome P-450 isoenzyme CYP 2E1 should impair alcohol metabolism. Also, as Zn is essential for ADH activity, further impairment could be expected with Zn deficiency. However, concentrations of rat liver NAD deaminates [NAD+ + NADH] are only partially decreased, by ~50%, in experimental niacin deficiency (Alencar and Moraes-Santos, 1991; Rawling et al., 1994). Levels in whole blood (Creeke et al., 2007) and erythrocytes (Raghuramulu et al., 1965) of pellagra patients are, however, normal. It therefore appears that depletion of the above dinucleotides is only partial, thus enabling ethanol metabolism to proceed. A severe depletion would be incompatible with cell viability and a depletion in pellagra patients stronger than that observed experimentally could limit alcohol metabolism and thereby cause accumulation of ethanol at cytotoxic levels. In alcoholics without pellagra, CYP2E1 induction is well documented (see, e.g. Lieber and DeCarli, 1970), whereas ADH activity may or may not be impaired, with severity of liver dysfunction determining the level of impairment (Cáballería, 2003). In experimental Zn deficiency, ADH activity is decreased, whereas that of aldehyde dehydrogenase is unaltered (Das et al., 1984). Despite a decrease in ADH in Zn deficiency, human alcohol metabolism remains unaltered (Asada and Galambos, 1963). Also, the Zn deficiency associated with chronic alcoholism is not correlated with alcohol metabolism (Vannucchi et al., 1995 and references cited therein). However, induction of Zn deficiency by alcohol can potentiate that induced by pellagra and the associated skin and neurological signs. Also, alcohol metabolism to acetaldehyde can induce a vitamin B6 deficiency leading to perturbation of Trp metabolism (see below), thus further contributing to pellagra incidence.

**Influence of alcoholism on Trp metabolism to niacin**

Trp metabolism in alcoholism has been studied mainly in relation to serotonin and its role in the mood changes and other psychiatric disorders associated with alcohol dependence, whereas fewer studies have addressed the kynurenine pathway (for reviews, see Badawy, 2002, 2005). The first and rate-limiting enzyme of this pathway, TDO, received the greatest attention, with changes in its activity in rats depending on whether ethanol is consumed acutely or chronically and if studies are performed during the chronic phase or subsequent withdrawal. In normal rats, acute ethanol administration activates TDO by a substrate (Trp)-type mechanism and evidence for a haem-mediated activation in human volunteers is based on an observed decrease in plasma [Trp] with no cortisol elevation (Badawy et al., 1995). By contrast, chronic alcohol administration inhibits rat liver TDO activity by an NAD(P) H-mediated allosteric mechanism, whereas subsequent withdrawal causes a corticosterone-mediated enhancement. Evidence for TDO inhibition in chronic alcoholism has been obtained in studies in chronic alcoholics during the chronic phase, i.e. within 24–48 h of cessation of alcohol intake, and includes decreased urinary excretion of kynurenine, 3-hydroxykynurenone and xanthurenic acid, increased cerebrospinal fluid [Trp] and decreased serum kynurenine at admission and upon
relapse 3 months after detoxification (for references, see Badawy, 2002, 2005). If the TDO inhibition in chronic alcoholics is also caused by the above reduced dinucleotides, it may be concluded that adequate amounts of the NAD⁺ and NADPH cofactors are available to facilitate ethanol oxidation. In other studies performed during the abstinence phase (2–3 weeks post-detoxification), changes in plasma [Trp] were consistent with TDO activation or at least a return to normal (see Badawy, 2002, 2005). Thus, TDO inhibition in chronic alcoholism before abstinence is the first potential mechanism of impaired niacin synthesis in alcoholic pellagra. In populations deficient in niacin, niacin formation from any marginal Trp intake could therefore be compromised by alcohol-induced TDO inhibition.

Shortly before the appearance of the alcohol-withdrawal syndrome in alcohol-dependent men, Badawy et al. (1998) observed a large increase in free serum [Trp] and a rise in cortisol. If TDO is also glucocorticoid-induced in humans during alcohol withdrawal, as in rats (see earlier), a potential increase in the excitotoxic and endogenous NMDA receptor agonist quinolinic acid would be expected, which may play a role in the hyperexcitability of acute alcohol withdrawal (Morgan, 1991).

Shibata (1990) studied enzymes of the kynurenine pathway beyond TDO in chronically ethanol-treated rats and found no change in kynureninase or in subsequent enzymes leading to niacin synthesis. However, in chronic alcoholics, kynurenine aminotransferase and kynureninase activities could be inhibited by acetaldehyde through binding of their pyridoxal 5′-phosphate cofactor, thus enhancing its degradation, as has been shown in rats (Crouch and Solomon, 1989). In addition to TDO inhibition, a potential inhibition of kynureninase, as suggested by an increased urinary excretion of xanthurenic acid (Payne et al., 1974), could further contribute to niacin deficiency in alcoholism. Vannucchi et al. (1982) demonstrated increased urinary excretion of 3-hydroxyanthranilic acid (Payne et al., 1974), which may play a role in the hyperexcitability of acute alcohol withdrawal (Morgan, 1991).

**Influence of alcohol on tryptophan availability to the brain**

The effects of alcohol on Trp availability to the brain, expressed as the plasma [Trp]/[CAA] ratio, are important in relation to serotonin synthesis and the incidence of depression in pellagra. As stated earlier, the reported (Truswell et al., 1968) decrease in the above ratio may explain the incidence of depression in non-alcoholic pellagra. Calculation of this ratio from data reported by Vannucchi et al. (1991) in alcoholic pellagra revealed an unpaired ratio, compared with controls, despite a decrease in plasma concentrations of all six competitors. However, the decrease in plasma [Trp] (29%) was relatively smaller than that in the 5 CAA (38–57%). A possible explanation is that, whereas these decreases reflect general protein malnutrition, the possible inhibition of TDO by chronic alcohol consumption may have partially mitigated the Trp depletion. It follows therefore that depression may not be a prominent, or at least a consistent, feature of alcoholic pellagra. From the data by Vannucchi et al. (1991), the [Tyr + Phe]/[BCAA + Trp] ratio in alcoholic pellagra is also not decreased, thus suggesting that cerebral catecholamine synthesis is also not impaired.

**Influence of alcoholism on haem metabolism**

Alcohol also exerts major effects on porphyrin and haem metabolism (for review, see Doss et al., 2000), which may further aggravate the skin and neurological changes in pellagra. Alcohol is one of many drugs contraindicated in patients with the porphyrias and is a major factor in porphyria cutanea tarda. In chronic alcoholics and rats treated chronically with ethanol, activities of several enzymes of the haem-biosynthetic pathway are inhibited, including 5-ALAD, uroporphyrinogen decarboxylase and coproporphyrinogen oxidase, whereas those of 5-ALAS and porphobilinogen deaminase are elevated (for references, see Doss et al., 2000). These enzymic perturbations result in abnormal accumulation of porphyrins, which may explain the exacerbation of skin features of cutaneous porphyria and possibly also those of pellagra. The induction of 5-ALAS and inhibition of 5-ALAD by alcohol are two very important effects, as both lead to accumulation of 5-ALA. Both effects are thought to be mediated by metabolic changes caused by ethanol metabolism disturbing the [NADH]/[NAD⁺] ratio (Badawy et al., 1989; Doss et al., 2000 and references cited therein). Zn (Gibbs et al., 1985) and thiamine (Hauschildt, 1975) deficiencies can also contribute additionally to the 5-ALAD inhibition in alcoholic pellagra. Thus, a potentiated elevation of 5-ALA can enhance the skin and neurological features of pellagra. 5-ALA levels in pellagra have not been studied, but alcohol intake by rats and porphyrin patients increases urinary [5-ALA] by 2–3-fold (Doss et al., 2000).

**Disturbances of glutamate and GABA neuronal activity**

As is the case with Trp metabolism, the effects of alcohol on functions of the excitatory amino acid glutamate and the inhibitory neurotransmitter GABA depend on the alcohol drinking status (acute, chronic or withdrawal) (for review, see Clapp et al., 2008). Briefly, acute alcohol intake inhibits NMDA receptor function and decreases glutamate release, but enhances GABAergic activity. These changes may account for the anxiolytic effects of acute alcohol consumption. With chronic alcohol consumption, there is a compensatory increase in (upregulation of) NMDA receptors and a decrease in GABAergic activity, resulting in a hyperexcitability state. As stated above, the endogenous NMDA receptor agonist quinolinic acid may be involved. This hyperexcitability can precipitate alcohol withdrawal seizures and the associated anxiety. Thus these alcohol-related changes could further impact the neurological features of pellagra.

**THERAPEUTIC ASPECTS**

The diagnosis and treatment of alcoholic and non-alcoholic pellagra have been considered in a number of reviews (Cook et al., 1998; Oldham and Ivkovic, 2012; López et al., 2013) and will not be discussed here. However, it is important to emphasize that many cases of pellagra encephalopathy go undetected, because of similarities with alcohol-withdrawal delirium (AWD). In chronic alcoholic patients, currently, emphasis is placed on the Wernicke–Korsakoff syndrome and the need to use thiamine as an essential treatment. Alcoholics are invariably malnourished and so their thiamine deficiency is very likely to be associated with deficiencies of other B
v vitamins, including niacin. Oldham and Ivkovic (2012) proposed the use of niacin as replacement (not supplement) along with thiamine and other B vitamins in AWD, and, when pellagra is suspected, niacin therapy should be started before laboratory investigation of the niacin status. From the above biochemical accounts, it is possible to outline the biochemical rationales for therapeutic intervention in pellagra and the associated alcoholism at multiple levels (Table 4). Niacin administration is essential for reversal of all pellagra symptoms, as is that of thiamine if alcohol is a contributing factor. However, treatment must also be accompanied by adequate protein nutrition.

GENERAL CONCLUSIONS AND COMMENTS

The present article has reviewed biochemical aspects of alcoholic and non-alcoholic pellagra. Niacin deficiency of many causes is the most important feature of pellagra followed by impaired conversion to niacin of the essential amino acid tryptophan. The skin disturbances in pellagra are almost certain to involve deficiencies of the histidine metabolite urocanic acid, the Trp metabolite picolinic acid and zinc. Depression in pellagra may be due to decreased cerebral serotonin synthesis caused by deficiencies of Trp and pyridoxine. The haem precursor 5-ALA and the Trp metabolite kynurenic acid may be involved in both the skin and the neurological disturbances. Alcoholism contributes to pellagra incidence through the associated malnutrition and B vitamin deficiencies, impaired conversion of Trp to niacin, induction of zinc deficiency and elevation of 5-ALA. Investigating the potential role of this haem precursor and other possible determinants, notably picolinic and kynurenic acids, may yield important information on biochemical mechanisms in pellagra.

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