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4-pyridone-3-carboxamide ribonucleoside triphosphate accumulating in erythrocytes in end stage renal failure originates from tryptophan metabolism

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Abstract We recently identified an erythrocyte nucleotide accumulating in end-stage renal disease as 4-pyridone-3-carboxamide ribonucleotide triphosphate (4PYTP), a nucleotide never described previously. Plasma tryptophan concentration has been previously reported to be reduced in patients in chronic renal failure that is in turn associated with elevated precursors of tryptophan metabolism, including L-kynurenine and quinolinic acid, both of which have been implicated in the neurotoxic manifestations of chronic renal failure. Here we compare mean erythrocyte 4PYTP, and plasma tryptophan concentrations, in controls and four patient groups with renal impairment (10 per group) and confirmed a reduction in plasma tryptophan in patients on dialysis that corrected with renal transplantation. We found: An inverse correlation between plasma tryptophan and red cell 4PYTP concentrations (R^2=0.44, P<0.001) when all patients were grouped together. Restoration of both tryptophan and 4PYTP concentrations to control values was only achieved following renal transplantation. 4PYTP was absent from erythrocytes in Molybdenum cofactor (MoCF) deficiency implicating aldehyde oxidase/dehydrogenase, a Molybdenum requiring enzyme. High 4PYTP erythrocyte concentrations in adenine or hypoxanthine-phosphoribosyltransferase deficient patients in severe uremia (113 μM and 103 μM), confirmed the lack of involvement of either enzyme in 4PYTP formation. We propose that 4PYTP is formed by a novel route involving the oxidation of the intermediates of NAD turnover from quinolinic acid by aldehyde oxidase.

Key words N-methyl-2-pyridone-5-carboxamide (2PY) • Picolinic acid • Picolinic acid dehydrogenase • Aldehyde oxidase • Renal disease • Renal transplantation • Uraemic toxicity • 4-pyridone 3 carboxyamide ribo nucleotide triphosphate • Haemodialysis • CAPD

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Introduction

The uraemic syndrome has been the focus of intense study, particularly since the advent of haemodialysis in the 1960's. Almost every facet of human metabolism is altered, or implicated, in some way [1]. Marked increments, up to 50 μM, have been noted in plasma concentrations of the two pyridine nucleotide (NAD) degradation products – N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY) – both of which are normally present in low concentrations (ca 1 μM) being cleared effectively by the kidney [2–4].

Marked changes in erythrocyte nucleotides have also been reported in severe renal disease, especially in both

ATP (adenosine triphosphate) and GTP [5]. ATP, is normally present in erythrocytes in concentrations ten-fold that of any other nucleotide (mean 1200±132 µM adults), but can double in renal failure, as can GTP [5]. Such elevation was attributed to stimulation of phosphoribosylpyrophosphate (PPribP) synthesis by the raised intracellular phosphate in uraemic erythrocytes [6]. Earlier, we reported identification by liquid chromatography and mass spectrometry of a hitherto unknown nucleotide, accumulating in erythrocytes in renal failure to concentrations approaching 40% that of ATP, as 2-pyridone-5-carboxamide ribonucleoside triphosphate (2PyTP) [4]. Since that time a number of more sensitive techniques have been used to confirm our initial data, these included Tandem Mass Spectrometry, Nuclear Magnetic Resonance (NMR), Infrared (IR) Spectroscopy and HPLC/Mass Spectrometry NMR [7]. These studies revealed that the nucleotide was not a 2-pyridone but a 4-pyridone derivative namely 4-pyridone-3-carboxamide ß ribonucleotide triphosphate (4PYTP).

In the present paper we address the question of just how and why this nucleotide is formed in the erythrocytes of renal failure patients. To do this we have drawn on our experience from much earlier studies in children with genetic disorders of nucleotide metabolism associated with immunodeficiency – adenosine deaminase (ADA), and purine nucleoside phosphorylase (PNP) deficiency, respectively – where examination of plasma and urine for possible precursors provided the vital clue enabling our identification of deoxy-ATP and deoxy GTP respectively in erythrocytes of children with these two immunodeficiency disorders [8]. For this reason we have measured the concentrations of purines, pyrimidines and pyridines in both the plasma as well as erythrocytes of the different RF patient groups to look for potential precursors and used patients with an inborn enzymatic deficiency, namely that of MoCF deficiency to elucidate a possible pathway for 4PYTP biosynthesis.

Materials and methods

Patients

Heparinised blood was obtained from patients attending the adult Renal Clinic at Guy's Hospital with renal failure of varying aetiology and on different forms of treatment. Written informed consent was obtained (with local ethical committee approval according to the Declaration of Helsinki): data used in this study were obtained from 10 patients with mild chronic renal failure (low clearance (LC) creatinine <300 µM), 10 on haemodialysis (HD), 10 on chronic ambulatory peritoneal dialysis (CAPD) and 10 studied three months post successful renal transplantation (Post-Tx). The patients in the above study were all given dietary advice to ensure a healthy balanced diet, but none received any vitamin supplements as a form of treatment.

Data from the previously published cases with MoCF deficiency is also included for comparison [4]. All MoCF deficient patients were analysed as part of their diagnostic work up after presenting with neonatal seizures and hypotonia. Although MoCF deficiency predisposes to xanthine crystal nephropathy [9] none of these patients had renal impairment at the time of investigation.

Methods

The methods used have been reported in detail previously [10]. Briefly, the heparinised blood was centrifuged immediately at 12,000 rpm for 1 min. The upper layer of the plasma was then transferred to 1.5 ml microcentrifuge tubes and frozen at -20°C, if not deproteinised immediately and analysed by reversed-phase chromatography (RPLC) as described below:

200 µl of plasma was added to 200 µl of 10% trichloroacetic acid (TCA) (Sigma-Aldrich, Gillingham UK Sigma-Aldrich, Gillingham UK) in a 1.5 ml Eppendorf whilst mixing vigorously on a vortex, spun at 12,000 rpm for 2 min in a Microfuge and the TCA in the supernatant back-extracted with water-saturated ether to a pH >5.0. 25 µl of this extract was then injected onto the RPLC system described [10].

For erythrocyte nucleotide extracts, the top 1/5 layer of packed cells (containing platelets, WBC) was discarded. Erythrocytes were washed twice with 0.9% saline and then deproteinised immediately using 10% TCA which was back-extracted with water-saturated diethyl ether immediately to pH >5.0 as above, and frozen at -20°C, if not analysed immediately by anion-exchange HPLC [11].

The above extracts were processed using either a Waters Millenium (Milford, USA) RPLC or HPLC System, the u.v. spectra being recorded at 254 and 280 nm using in-line diode-array detection as described [10]. Data was analysed using the statistical computing package included in SigmaPlot v4.01, correlation statistics were performed using the statistics programme JMP (SAS software, USA).

Results

Nucleotide analysis by HPLC highlighting the unusual nucleotide in erythrocytes of CAPD patients

Of the four renal failure groups studied 4PYTP concentrations were highest in the CAPD group (Table 1), mean concentrations being more than 8-fold that of the LC group, and 30-fold controls ($P<0.001$). Mean 4PYTP concentrations were not altered significantly by either dialysis regime (mean pre HD 69 µM, post HD 62 µM), although concentrations were lower in the HD than the CAPD group. Compared with the control group, the elevation of 4PYTP in patients on either dialysis regimen was highly significant (Table 1; $P<0.001$). In contrast to the dialysis groups, the patients who had undergone successful renal transplantation showed near normal levels of erythrocyte 4PYTP.

Table 1 Plasma creatinine, tryptophan and erythrocyte 4PYTP concentrations (μM) control subjects and four patient groups (low renal clearance, pre haemodialysis, CAPD and post transplant) are listed (mean±SD, n=10 per category). Patients in both dialysis groups show a highly significant drop in plasma tryptophan and rise in red cell 4PYTP that is corrected in the post transplant group.

Patient group	Plasma creatinine, μM	Plasma tryptophan, μM	Red cell 4PYTP, μM
Control	80±8.61	49±6.26	5.8±0.55
Low clearance	142±72.1	39±7.11	19.9±15.7
CAPD	743±157	30±7.21	202.8±24.2
HD pre	1156±298	16±6.93	50.1±24.2
Post transplant	137±43.6	76±15.7	9.5±6.7

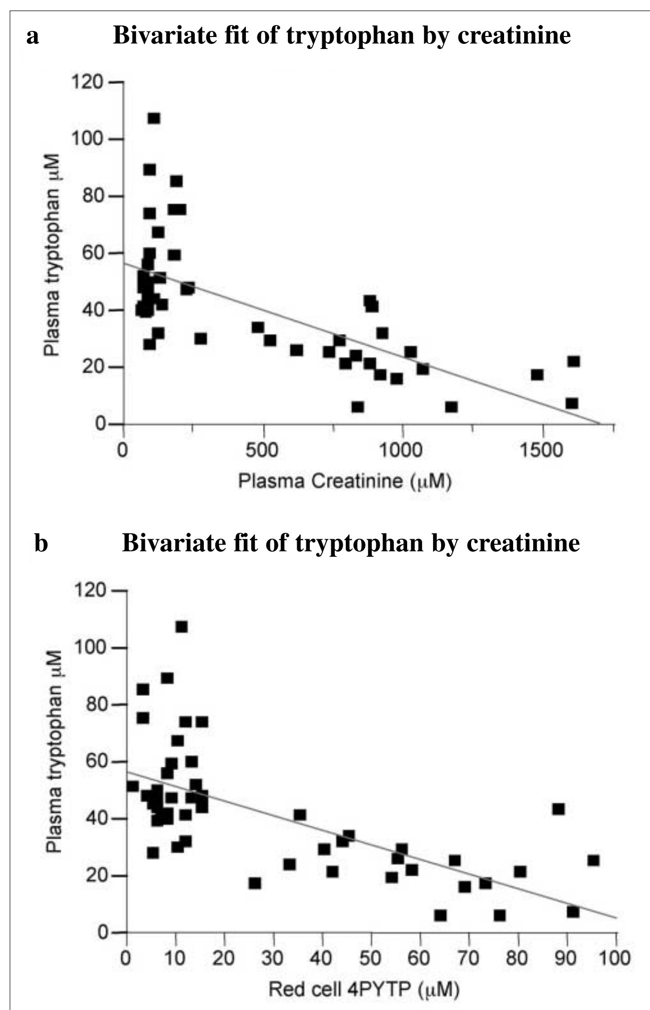

Fig. 1a,b Data from controls and all patients groups were combined. **a** Demonstrates the inverse correlation between plasma tryptophan and creatinine concentrations (R^2=0.47, P<0.001). **b** Demonstrates the inverse correlation between red cell 4PYTP and serum creatinine (R^2=0.44, P<0.001)

Plasma Tryptophan concentrations (μM) are inversely proportional to erythrocyte 4PYTP

As plasma tryptophan concentration has been reported to be reduced in patients with chronic renal failure we next explored the concentrations of tryptophan in our patients. Mean plasma tryptophan concentrations in the different renal failure groups are listed in Table 1. Figure 1a shows that when all the patients and controls are grouped, there is an inverse correlation between plasma tryptophan and creatinine concentrations (R^2=0.47 P<0.001) (Figure 1a) in keeping with findings from previous groups [12, 13].

Similarly when the relationship between red cell 4PYTP and plasma creatinine is analysed for all patients and controls (Fig. 1b) there is an inverse correlation (P<0.001). This is despite the haemodialysis group having a higher plasma creatinine but a lower red cell 4PYTP concentration compared to the CAPD group as shown in Table 1. The data is analysed and displayed using JMP.

Nucleoside and base analysis in plasma by RPLC

No identifiable precursor for 4PYTP was found in the plasma, suggesting initially that the nucleoside from which 4PYTP originates [14], must result from a precursor taken up rapidly from the plasma, or be formed within the erythrocyte. Alternatively, the precursor may be labile and broken down during the TCA acid extraction step.

Erythrocyte 4PYTP is absent in patients with Molybdenum co-factor deficiency

Figure 2 depicts the triphosphate section of an HPLC trace of an erythrocyte extract processed as described above and recorded at 254 nm of an unusual nucleotide, 4-pyridone-3-carboxamide triphosphate 4PYTP (24.0 min) illustrating the grossly elevated concentrations in CAPD (Fig. 2a), low concentrations in controls (Fig. 2b), but total absence in molybdenum co-factor (MoCF) deficiency (Fig. 2c). Note the elevated ATP and GTP also in CAPD, as reported previously [4].

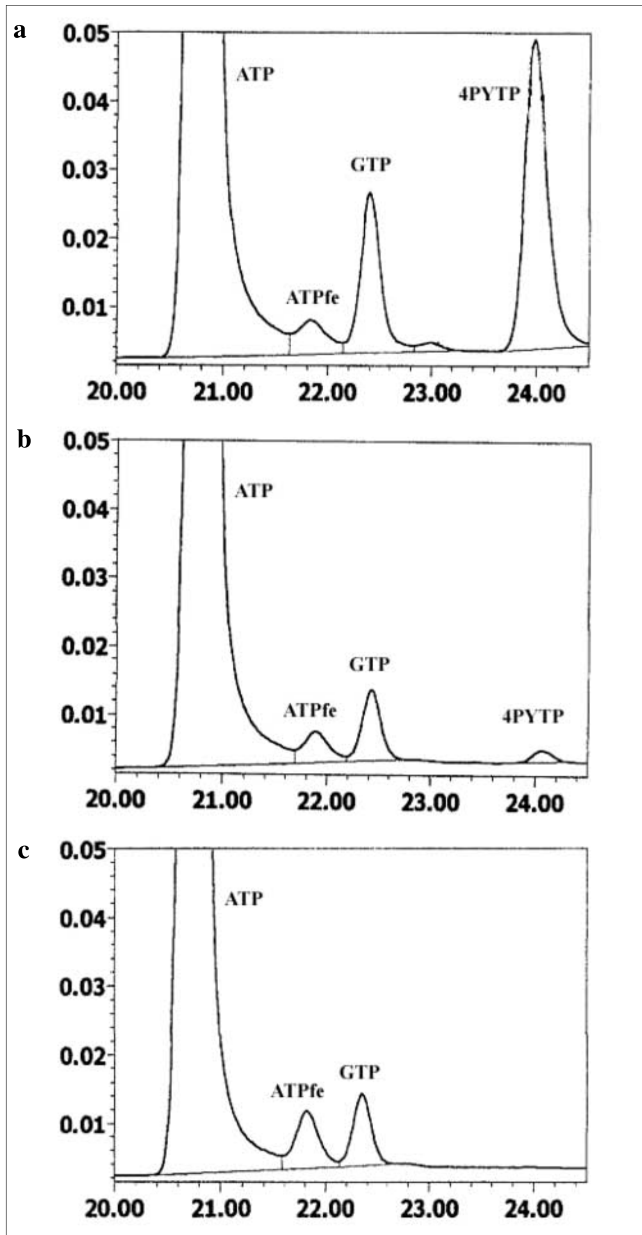

Fig. 2 High concentrations of 4PYTP in erythrocytes of a CAPD patient (**a**), contrast with the low concentrations in controls (**b**), and total absence in MoCF deficiency (**c**). HPLC traces were recorded between 20 and 25 min at 254 nm and 0.05 Absorbance Units Full Scale. HPLC conditions were adjusted to ensure a clear separation between, ATP (20.7 min, GTP (22.4 min) and 4PYTP (24 min)

Discussion

Severe plasma tryptophan depletion, is evident in our cohort of patients with renal disease, a consistent finding in renal failure of any cause, first noted by others a quarter of a century ago [12, 13]. Importantly, although the patient cohort with the highest red cell 4PYTP was not the cohort with the lowest plasma tryptophan, when all patients were grouped, plasma tryptophan showed a significant inverse correlation with red cell 4PYTP (Fig. 1). This inverse relationship suggested an alternative explanation for the route of formation of 4PYTP to that previously proposed [4]. Namely, that 4PYTP is not an NAD degradation product, but a tryptophan degradation product formed via the quinolinic acid synthetic route of NAD formation [15, 16] (Scheme 1), the last step of which, is catalysed by the enzyme quinolinate phosphorybosyl transferase (QPRTase, enzyme No 7 in Scheme 1). The high 4PYTP concentrations (113 μM and 103 μM respectively) in two patients with severe renal disease due to accumulation of 2.8-dihydroxyadenine, or gross uric acid overproduction in genetic deficiencies of adenine and hypoxanthine phosphoribosyltransferase deficiency respectively, exclude involvement of either purine base salvage enzyme in 4PYTP formation (data not shown), supporting our suggested involvement of QPRTase.

The origin proposed here for 4PYTP could explain (a) why 4PYTP also correlates with plasma creatinine, as well as (b) the corresponding rise in plasma tryptophan concentrations when these two parameters fall to concentrations within the control range after successful renal transplantation. The inverse relationship between tryptophan and 4PYTP supports 4PYTP as being a tryptophan-derived product. Quinolinic acid concentrations are also known to be elevated in renal failure [13, 17], due partly to inhibition of the enzyme catalysing the alternative route of tryptophan degradation via aminocarboxymuconate semialdehyde cearboxylase [13] (Scheme 1). Free picolinic acid and quinolinic acid are both found in normal plasma together with their respective amides [18]. In the present study the HD patients have lower levels of erythrocyte 4PYTP compared with the CAPD group (Table 1). This may be explained by the finding that quinolinic acid is very efficiently cleared by haemodialysis [13].

Two questions arise; firstly, how is 4PYTP formed from quinolinic acid in renal failure erythrocytes? Secondly, what MoCF dependant enzyme is critical for the formation of 4PYTP? Quinolinic acid elevation could result from a block in further metabolism, thereby explaining why erythrocyte NAD concentrations are low, or low normal (not shown) in renal failure, a finding also noted in an animal model of renal failure [19]. The proposed route of 4PYTP formation via tryptophan degradation shown in Scheme 1 involves a dehydrogenase such as aldehyde dehydrogenase also an Mo requiring enzyme [20, 21], consistent with the absence of 4PYTP in erythrocytes of the patients with MoCofactor deficiency [4, 20] and present in human blood [22, 23].

Interestingly, there are striking similarities between the bifunctional pyridine enzyme QPRTase converting quinolinc acid to NAMN (Scheme 1), and its companion pyrimidine enzyme UMPS (also an erythrocyte enzyme). Both, catalyse sequential steps in a two step reaction, the first

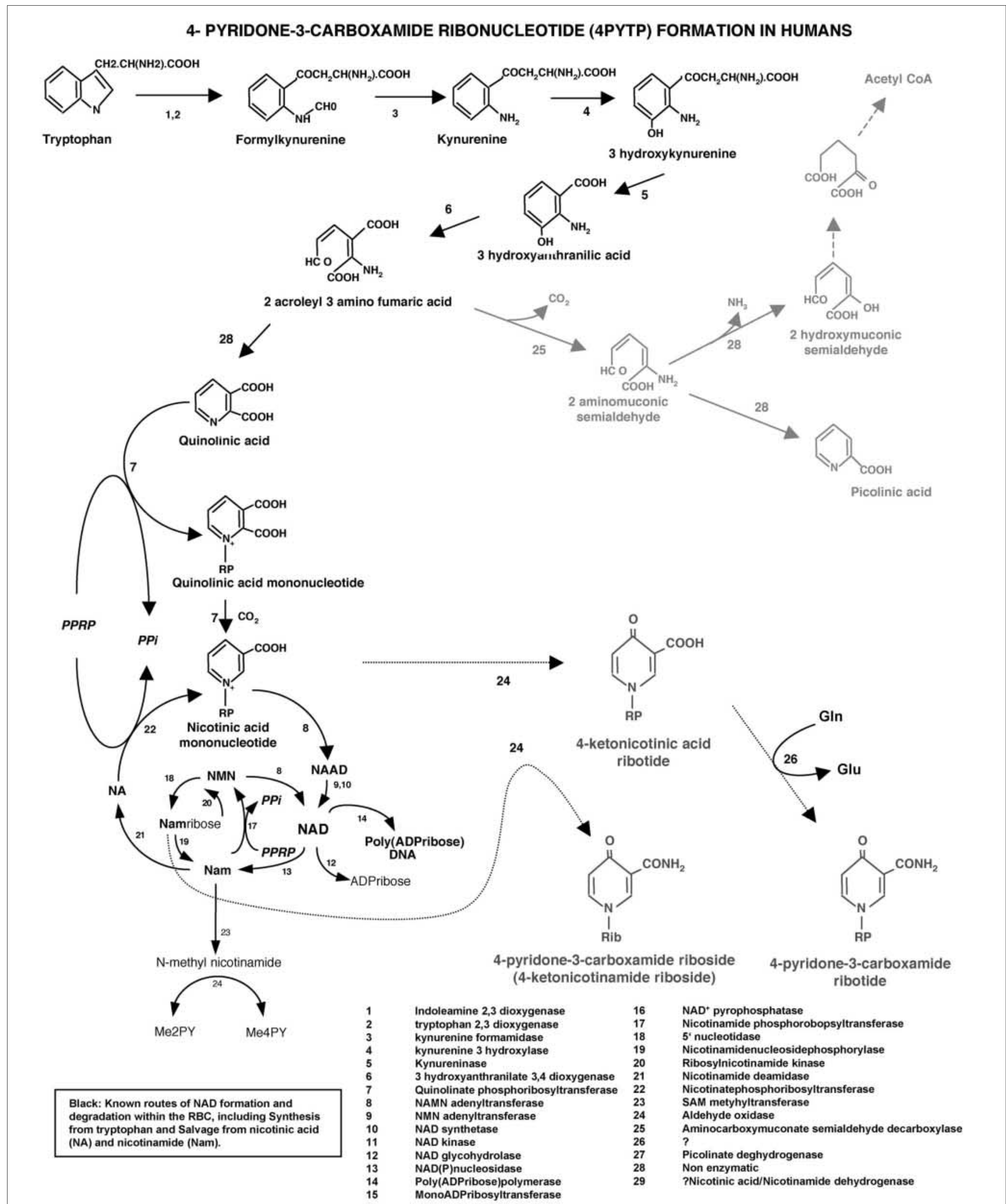

Fig. 3 Routes of NAD synthesis from tryptophan or breakdown to N-methyl-2-pyridone-5-carboxamide (2PY), or N-methyl-4-pyridone-5-carboxamide (4PY) respectively, highlighting the importance of the two molybdenum-requiring enzymes, (a) picolinic acid dehydrogenase in picolinic acid formation and (b) aldehyde oxidase (AOX) in 2PY/4PY formation. The enzymes involved are listed on the right. *Na,* nicotinic acid; *NaMN*, nicotinic acid mononucleotide; *Nam*, nicotinamide; *NMN*, nicotinamide mononucleotide; *PPRP*, phosphoribosylpyrophosphate

enzyme being a PRTase, dependent on PPRP [6] leading in the case of UMPS to the intermediate orotidine monophosphate (OMP); in the case of QPRTase to formation of quinolinic acid mononucleotide (QAMN), the second reaction involves a decarboxylase. A block in the second step of UMPS leads to increased orotidine formation derived from OMP by a specific erythrocyte nucleotidase [24]. QPRTase has been reported in mature erythrocytes and platelets and appears to be unaffected by renal failure [23] and like UMPsynthase catalyses a two step reaction in which the nucleotide quinolinic acid mononucleotide (QAMN) is formed first. Once formed, QAMN is normally rapidly decarboxylated to form nicotinic acid mononucleotide (NAMN), which is also an intermediate in the salvage route of NAD formation (Fig. 3) [25]. Importantly, plasma quinolinic acid concentrations are elevated in renal failure [13].

We suggest that when QA is in excess, as in renal failure, there is increased formation of QAMN in both the liver and within the erythrocyte driven by the increased concentration of PRPP [8]. QAMN is then decarboxylated at the 3 position to form nicotinic acid mononucleotide (NAMN) mononucleotide. Within the liver NAMN is fed into the NAD synthetic pathway (Fig. 3 in blue). Alternatively the nucleotide could then be oxidised in the erythrocyte by aldehyde dehydrogenase to its 4-keto derivative (Fig. 3 – dotted lines) and converted to its respective amine: nicotinamide mononucleotide – the reaction being driven by the excess nitrogen that is a feature of the uraemic state (Fig. 3). Consequently, the novel nucleotide, 4-ketopicolinamide ribotide, is formed first within the erythrocyte and subsequently triphosphorylated, as for ATP/GTP, thereby trapping it, the concentrations reflecting the severity of the renal disease.

This suggested route of 4PYTP formation could in turn explain some of the disturbing facets of the uraemic syndrome. Picolinic acids and quinolinic acids are known to have many serious clinical consequences *in vivo* in humans [12, 17, 26, 27]. Increased levels of quinolinic acid have been invoked to explain both the neurological manifestations of uremia [28], and the reduced secretion of erythopoetin in chronic renal failure [17]. Thus, formation of 4PYTP via the alternative route of tryptophan metabolism proposed, leading to accumulation at concentrations in excess of 250 μM (sometimes >0.5 mM in CAPD patients), would add credence to the suggestion that 4PYTP could be a uraemic toxin [4].

In summary, we propose that the inverse correlation demonstrated here between plasma tryptophan and erythrocyte 4PYTP concentrations (Fig. 1) in the different renal failure groups, supports the novel route of formation of the latter proposed in Scheme 1. This route involves QPRTase, and aldehyde dehydrogenase both of which are present in many tissues including the human erythrocyte [13, 22, 23, 29, 30]. The reaction is driven by the uraemic state at multiple levels: the elevated concentrations of quinolinic acid, increased nitrogen availability for the formation of the amides and finally the metabolic changes stimulating PPRP synthesis – previously invoked to explain the elevated ATP in renal failure erythrocytes [6].

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