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Review Article

Isoniazid Induced Toxicity: Systemic Lupus Erythematosus

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Abstract

Isoniazid is still, 60 years after its introduction, a main front line drug for treating tuberculosis. Isoniazid, a hydrazine compound, is metabolized through *N*-acetylation by the arylamine *N*-acetyltransferase (NAT) enzyme in humans and its metabolism was important in establishing the early observations on pharmacogenetics since its metabolism to *N*-acetylisoniazid was identified as being genetically controlled. The incidence of adverse side effects to isoniazid is also linked to its metabolism. These side effects include liver toxicity, neuropathy and a condition resembling the auto-immune disorder Systemic Lupus Erythematosus (SLE). The latter side effect shares similarities with side effects to hydralazine, an anti-hypertensive, which is also a hydrazine and, like isoniazid, induces SLE-like symptoms in a sub group of patients who are almost exclusively slow NAT acetylators. The complement system in humans is essential for immune complex clearance and the chemical mechanism by which isoniazid and hydralazine interact with the activation of the complement cascade has been established, demonstrating their interference with the activation of the thiol ester in complement component C4 such that immune complexes become deposited at inappropriate tissue sites in the small blood vessels, kidneys and joints, thereby generating a SLE-like condition. The relevance of immunohistocompatibitility types relating to the polymorphic C4 type is also explored.

ABBREVIATIONS

ADPR: Adenosine Diphosphate Ribose; HLA: Human Leukocyte Antigen; NAD: Nicotinamide Adenine Dinucleotide; INH: Isoniazid; InhA: enoyl-[acyl-carrier-protein]-reductase; SLE: Systemic Lupus Erythematosis; TB: Tuberculosis

INTRODUCTION

Isoniazid (INH) was first introduced for the treatment of tuberculosis (TB) in 1952. It has revolutionized treatment of TB, usually in combination with other drugs [1]. Nevertheless there is a growing search for new anti-tubercular therapies following the availability of genomic information and identification of possible new anti-tubercular targets [2,3] with new treatments reaching the clinical trials stage as part of a growing pipeline of novel anti-tuberculars [4]. Although drug resistance is a growing and real problem, INH is still a front line treatment in combined therapies [5]. The mechanism of action of isoniazid is important as it is one way of identifying new drug treatments [6,7] and resulted in the identification of the agent ethionamide [8]. With INH, the drug is activated by oxidation by KatG (Figure 1), inside the mycobacterial cells and the resulting activated moiety then forms an adduct with NAD^+ [8].There is now a consensus that the adduct inhibits the enoyl-[acyl-carrier-protein]-reductase (InhA) [9] and thus inhibits synthesis of the mycolic acid component of the mycobacterial cell wall. There was an earlier controversy as to the nature of the inhibited enzyme and a more recent study has used computational methods to investigate the range of targets for the adduct [10]. Understanding of the molecular changes which lead to isoniazid resistance [11], have been important not only in understanding resistance but also in understanding the mechanism of action of this mainstay of anti-tubercular therapy and of identifying new possible treatments [6,7,12].

Whilst INH is still a front line treatment and is the drug of choice for latent TB, it is however a drug which has been associated with a wide range of adverse side effects. The most common of these is hepatotoxicity [13], followed by neuropathy [14], and also a condition resembling systemic lupus erythematosus (SLE) [15,16]. The mode of action of isoniazid oxidation results in the formation of a covalent bond with NAD^+. The effectiveness of isoniazid in combating TB and its mode of action being is the "yin" to the "yang" in relation to its side effects. This review focuses on one particular side effect induced by isoniazid, namely systemic lupus erythematosus (SLE). The condition of drug-induced lupus is shared with a wide range of other drugs [17], and has also been reviewed recently in an excellent online article which sets out the facts [18].

The most common other drugs associated with SLE include the anti-hypertensive, hydralazine, the anti-arrythmic procainamide

(which is still used in the USA but only in special circumstances in the UK) and also the anti-arthritic drug penicillamine.

Isoniazid and hydralazine are chemically similar, both being hydrazine compounds (Figure 2), and this review focuses on a the nature of SLE induced by isoniazid, using examples derived from isoniazid's interaction with the immune system in comparison with hydralazine also.

The emergence of HIV and concommitant increase in TB, including paediatric TB [19], has resulted in an increased interest in isoniazid toxicity and this has been particularly important in relation to understanding the presentation of instances where children have suffered adverse side effects [14].

ISONIAZID USE

Isoniazid is still the main front line drug against tuberculosis, despite the growing problem of resistance. It is usually used in combination with other anti-tuberculars for latent TB and in ongoing drug regimens [20-22]. In addition, isoniazid is being used prophylactically in latent TB [23], and it has been studied in relation to treatment of children who are not receiving anti-viral agents for HIV and appears to have a positive effect in reducing deaths from TB.

INH resistance in TB has been widely studied and the overwhelming evidence suggests that mutations in the *InhA* gene and the *KatG* gene account for the majority of the incidences of resistance in clinical isolates [11,12], but in addition mutations in the gene encoding for the mycobacterial pumps and in the *arylamine N-acetyltransferase* (*nat*) gene in mycobacteria have been implicated. The latter two appear to have a minor effect [11,24-26].

PATTERN OF SIDE EFFECTS

SLE is one of the less common side effects of isoniazid therapy. The diagnosis relies on the appearance of a combination of a range of indicators such as rash, joint involvement, and is particularly linked with the appearance of autoantibodies [27-29], which have been noted in a similar fashion to hydralazine and procainamide induced SLE [30-32]. One of the key features of the diagnosis of INH-induced SLE has been the recovery and reversal of symptoms on removal of the drug and predictive assays have been reported relating to the induction of autoantibodies [15,28], such as the antibodies identified against the DNA H2A-H2B complex [28]. A predictive test involves a popliteal lymph node activation test and has been reported to be useful in both isoniazid and procainamide adverse reactions [33].

EFFECTS O METABOLISM

It has been proposed that the oxidation or peroxidation of INH and also of hydralazine are important in the development of the idiopathic immune response [34], however there is overwhelming evidence that isoniazid is metabolized in humans by *N*-acetylation [35-37]. *N*-acetylation of INH was amongst the first examples of pharmacogenetic variation to be identified [35] and the molecular basis of the variation in acetylation now extends to over 90 alleles [38]. The original observation that SLE was associated with slow *N*-acetylation of hydralazine [31,39-42] and INH [43], has been substantiated by extensive genotyping studies in different populations [15,32]. The implication is that the difference in the clearance of the drug in slow NAT acetylators creates sufficient of a non-acetylated metabolite to be involved in the adverse reaction. The competition between NAT-acetylation and KatG-activation of INH in humans has also been described in mycobacterial cells themselves [44]. It was demonstrated that mycobacterial cells have an enzyme which *N*-acetylates INH [26,45], and this has also been demonstrated to contribute to sensitivity to INH in mycobacterial gene deletion and overexpression studies [44,45]. Genetic mutations in the *nat* gene in clinical isolates of *Mycobacterium tuberculosis* [11,24,25], have demonstrated that whilst the *nat* gene does show mutations it makes a minor contribution clinically to INH resistance with the mutations in *InhA* and *KatG* genes being of most importance [11,12]. Whilst genetic variation in the mechanisms for pumping INH from the mycobacterial cells has also been identified, but it has also been found to contribute only marginally to the overall INH resistance [11,12].

Structural studies on NAT enzymes from mycobacteria in which each NAT protein has a very similar amino acid sequence [46] have demonstrated INH in the binding pocket of the NAT enzyme from *M. smegmatis* [47]. In a separate study, hydralazine has been located in the binding site of the NAT enzyme from *M. marinum* [48], which has shed light on the reaction mechanism for *N*-acetylation. Interestingly the *nat* gene itself and the operon in which it is found is essential for mycobacterial survival inside cells [45] and has been explored as a target for antibacterial therapy [49-51].

MECHANISM OF THERAPEUTIC ACTION AND ADVERSE REACTION

Isoniazid is activated inside macrophage and the enzyme KatG which catalyses the activation is essential for the action of isoniazid (Figure 1).

Once it is activated, the moiety forms a covalent interaction with NAD^+ and the adduct formed gives rise to a complex which stops InhA working in the formation of mycolic acids [9].

It has been argued that the adverse reaction in humans is caused by an oxidation reaction perhaps in activated macrophages [34]. It is clear that there is a sub population of individuals who are susceptible to drug-induced SLE. Not all individuals get the adverse reaction. The incidence of INH-induced SLE is low (much less than 5%) although in hydralazine-induced lupus the incidence is higher with up to 12% in the early days when higher doses were used [31,41]. In order to understand the contribution of genetics, studies have been carried out to investigate the Human Leukocyte Antigen (HLA) type of patients who experience SLE-like symptoms. These studies have identified that individuals who carry the HLA DR4 type are more prevalent in the adverse reactors [52], along with those who are slow acetylators for NAT. In addition to the HLA DR4 type, it has been observed that there is an increased incidence of side effects on individuals carrying the C4A-null type - a class 3 HLA antigen [53]. It is well established that deletion of the genes for the early components of the classical pathway of complement are at increased risk of developing SLE and the C4A-null type is a particular risk feature [54]. These studies have been confirmed for hydralazine-induced SLE in

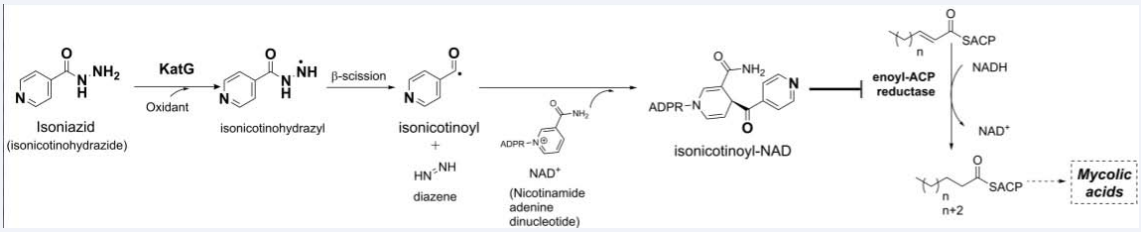

Figure 1 Mechanism of action of Isoniazid. Isoniazid is a prodrug which can be activated by the catalase-peroxidase KatG. The activated form (isonicotinoyl) reacts with NAD+ to form the adducts isonicotinoyl-NAD which inhibit the target NADH-dependent enoyl-ACP reductase involved in the fatty acid synthase type II system; this results in mycolic acid biosynthesis inhibition and mybacterial cell lysis. Based on [8,9]. ADPR= adenosine diphosphate ribose.

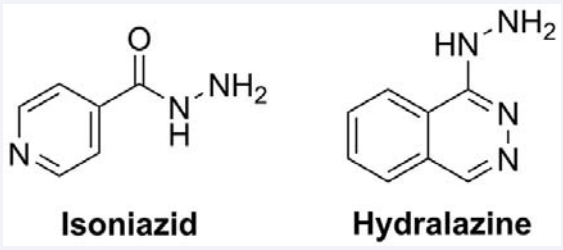

Figure 2 Comparison of the chemical structures of isoniazid and hydralazine.

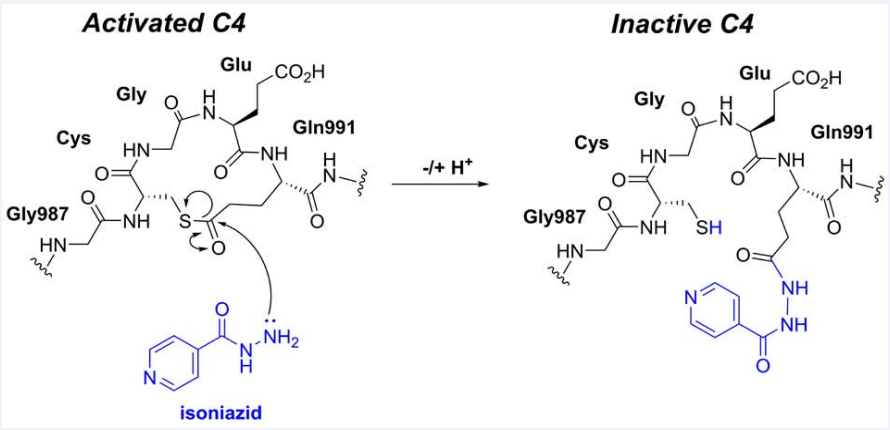

Figure 3 Isoniazid inhibition of complement component C4.
When C4 is activated by immune complexes and also by subcellular debris *via* the classical or lectin pathways of complement the C4 is cleaved by either C1s or MASP2 and the thiolester which is within the C4 structure is activated through a conformational change. The exposed short lived thiol ester can bind to either hydroxyl or amine groups on the activating surface but this binding can be inhibited by the presence of a nucleophile and isoniazid itself can become bound to the active site *via* an amide bond [64-66].

the clinic [52-54]. In addition, noting that it is the drug rather than the *N*-acetylated metabolite which is the likely causative agent, a study showed that hydralazine but not its *N*-acetylated metabolite will bind to C4 when C4 is activated [55], in effect creating a chemical knock out of C4. In addition, the C4A type is more susceptible to this inhibition that C4B [56]. The inhibition reaction occurs on activation of the crucial thiolester in C4 [57], and results in the drug becoming bound to the complement component *via* the activated thiolester [56]. This in turn hinders the amplification of the complement cascade such that binding of the main component C3 does not occur. It has been demonstrated that immune complexes which are bound in joints and kidneys in drug-induced SLE have a reduced binding of C3 [58,59].

The mechanism of INH inhibition of C4 activation is shown in Figure 3. Other polymorphisms in complement receptor type 1 affecting the handling of immune complexes have also been investigated in hydralazine-related SLE cases [60-63].

DISCUSSION & CONCLUSION

Isoniazid is still a front line drug of choice in tuberculosis treatment. It is metabolized by *N*-acetylation in humans. Adverse side effects are associated with a genetic sub group of individuals in particular the slow NAT acetylators, although no distinct *NAT* allele has been specifically identified. SLE is a rare side effect in

INH treatment. The disruption of immune regulation which leads to SLE can be associated with the ability of INH and the chemically similar anti-hypertensive agent hydralazine, to form a covalent inhibitory reaction with complement component C4, which is likely to result in an inability to clear immune complexes.

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