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Possible chemical initiators of cognitive dysfunction in phenylketonuria, Parkinson's disease and Alzheimer's disease

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ABSTRACT

Though a great deal is known of the pathophysiology of phenylketonuria (PKU), Parkinson's disease (PD) and Alzheimer's disease (AD) very little is known regarding possible chemical species responsible for initiating the cascade of events that ultimately cause cognitive dysfunction. Can these be viewed as inborn errors in metabolism, occurring at various stages in the life cycle, analogous to adult onset diabetes? One major deficiency in understanding such conditions is the paucity of information regarding the total metabolic pathway for various amino acids that may be implicated in their causation.

For example in PKU, its etiology was reported in 1934 and dietary restriction of phenylalanine proved effective for individuals with unsatisfactory metabolism of phenylalanine. Yet, current phenylalanine metabolism does not take into account fully the multiple biochemical pathways operating whose role is preventing burdensome accumulations of intermediates that can contribute to morbidity and toxicity. The same may apply for metabolism of tyrosine in PD and methionine in AD.

Especially important, are the presence of labile and reactive chemical species which may be causative agents in protein alteration, misfolding and the creation of prions in neurodegenerative diseases, thereby preventing normal protein catabolism and excretion. Though genetic or epigenetic factors must be responsible, the question remains how are these translated into the chemical structures responsible for disease initiation? The purpose of this presentation is to explore potential labile metabolites in those biochemical pathways, which may be contributing factors.

Finally it is worth noting, that drug development has been increasingly designed based upon targeting genetic deficiencies. The effectiveness of this approach for the treatment of these neurodegenerative illnesses will be determined in the future.

Introduction

The clinical manifestations of phenylketonuria (PKU) [1,2]. Parkinson's Disease (PD) [3] and Alzheimer's Disease (AD) [4] are well known. However, little is known regarding possible chemical species responsible for initiating the cascade of events which ultimately causes cognitive dysfunction. One major deficiency in understanding such conditions is the paucity of information regarding the total metabolic pathways for various amino acids that may be implicated in their causation.

Especially important, are the presence of labile and reactive chemical species (i.e. oxidative stress) which may be causative agents in protein alteration, misfolding and the creation of prions in neurodegenerative diseases [5]. Such transformations prevent normal protein catabolism and excretion. Though genetic or epigenetic factors must be responsible, the question remains how are these translated into the chemical structures responsible for disease initiation? The purpose of this presentation is to explore potential labile metabolites in those biochemical pathways, which may be contributing factors.

It has been proposed [6,7] that PKU, PD and AD may resemble one another with the formation of toxic fibrils that are found in the brain. These structures are not metabolized and their presence is associated with abnormal neuronal activity causing cognitive dysfunction. With the exception of PKU, most of these diseases are chronic, occurring later in life. The overriding question is why does this occur only with a certain subset of the population while others may live a normal life span without any evidence of cognitive failure? A second critical question is what could be the chemical initiators of such morbidity and is there some commonality among these in other neurodegenerative diseases? One possibility is that the alteration of normally occurring proteins may be an important factor in neurodegenerative diseases. Once altered, proteins can exhibit changed metabolism and excretion patterns, impaired enzymatic activities, disruption of existing

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cellular architecture or become targets for degradation. Such modifications can contribute directly to neurodegeneration and offer the potentiality of spreading as pathogenic prions. If so, a unifying hypothesis for such diseases may be at hand [5].

In this presentation, we shall be focusing on the possible chemical initiators of these diseases since, in many instances, their identity and syntheses remain to be established. One may have assumed that all compounds formed in the biochemical pathways of various amino acids, possibly involved in these diseases, have been isolated and fully characterized. Unfortunately, that is not necessarily the case especially for those intermediates that are highly reactive and quite unstable. And yet, such compounds are precisely the ones which must be evaluated for their potential to form and react covalently to alter proteins.

It is our intention to examine each of these three diseases with that objective in mind. While this will not be exhaustive, it may point the direction that should be undertaken in understanding the chemical origins of these and other related neurodegenerative diseases. Probing the chemical initiators may be an important first step in understanding disease pathogenesis by identifying metabolic pathways that can lead to the accumulation of pathogenic metabolites. Such an understanding could provide the basis for creating therapies in their treatment or prevention.

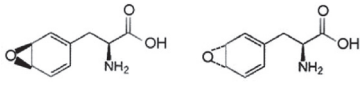
One final point that needs to be stated is that in mammalian biochemistry there are multiple pathways involved in metabolism. These may be present to prevent the accumulation of a single species whose excess might contribute to undesired toxicity. Though some pathways may be of minor importance, nevertheless their existence, and the various circumstances under which they are utilized collectively, ensure normal homeostasis. However, aberrations in their utilization can lead to accumulation of toxic metabolic intermediates.

Phenylketonuria

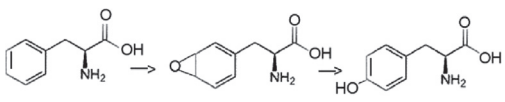
Phenylketonuria (PKU) is classified as an autosomal recessive genetic disorder characterized by a gene mutation involving the hepatic enzyme phenylalanine hydroxylase [8]. Phenylalanine (phe) restriction is beneficial for PKU patients, but the mechanism by which unrestricted phe consumption contributes to pathology remains unresolved. The specific questions remaining are: what phe metabolites accumulate in PKU patients and by what mechanism does their accumulation contribute to pathology?

Phenylalanine hydroxylase, which is responsible for the metabolism of phe to tyrosine, requires tetrahydrobiopterin as a cofactor. Since the enzyme is a hydroxylase, this implies that a hydroxyl group is inserted directly into phe in the generation of tyrosine without any oxygen intermediates.

Another possible metabolic pathway for converting phe to tyrosine involves the 3,4-epoxide. This supposition is based on the observed metabolism of benzene biologically with the isolation and characterization of benzene epoxide [9]. Also, the epoxide of phe is proposed as an intermediate [10] and studies in man using deuterated L-phenylalanine confirm its existence in the formation of tyrosine [11].



Scheme 1. Structure of the two epoxides of phenylalanine.



Scheme 2. Phenylalanine → phenylalanine epoxide → tyrosine.

Thus, both pathways appear to be possible. However, neither of the two possible isomers (α, β) of the 3,4-epoxide of phe, has been synthesized. Yet, it is eminently reasonable that they might be intermediates in the metabolism of phe in PKU (Scheme 1).

If such structures are intermediates, implicitly it means that there are epoxidases involved in their formation and epoxide hydrolases in their conversion to tyrosine as shown in Scheme 2.

These, as other epoxides, have the potential to act as nucleophiles binding covalently to various amino acid *R*-groups (OH, NH or SH) on a protein molecule. Modified naturally occurring proteins can acquire novel structural properties or activities and their normal degradation might be impeded. As a result, they might acquire prion-like properties. Alternatively, normal protein degradation might be enhanced leading to the loss of vital proteins.

In essence, the chemical initiators for protein modification may be the epoxides and their persistence and slowness in their ability to undergo the NIH shift to form tyrosine may be a contributing cause for phenylketonuria. Obviously, this is a hypothesis. It can be proved or disproved with the preparation of the epoxides, their full characterization and a determination whether such structures are intermediates in metabolism that result in phenylketonuria.

In order to probe the question of the origin of the oxygen species in tyrosine derived from phe, it would be relevant to do O-18 studies and determine whether the oxygen atom in tyrosine was derived from molecular oxygen or water and whether there are differences in patients having phenylketonuria.

Maternal phenylketonuria syndrome describes the teratogenic effects that result in mental retardation, microcephaly, congenital heart disease and intrauterine growth retardation in the fetus, occurring up to 90% when a pregnant PKU mother is not maintaining very low levels of phe in her blood. This occurs despite the fact that the fetus may only be a carrier of the recessive gene [12].

While the pathogenesis is unknown, one can envisage that aberrant maternal metabolites, such as epoxides, can cross the placenta because of their small size, causing deleterious effects systemically in the fetus. This may be a more likely scenario than invoking phe inhibition of the transport of other neutral amino acids across the placenta, or direct toxicity by phe itself.

Parkinson's disease (PD)

Though the precise chemical initiators of PD still remain to be determined, there has been speculation as to a possible chemical origin for PD [3]. One entity involves an epoxide of tyrosine, which can be viewed as an immediate precursor of L-dihydroxyphenylalanine (L-DOPA).

Such epoxides and their respective epoxide hydrolases must be genetically determined. However, none of the epoxides shown in Scheme 3 have been synthesized and therefore, it has not been determined whether any are intermediates in the formation of L-DOPA or whether they are actively transported into the CNS. And obviously, it is unclear what effect, if any, this epoxide has on L-DOPA production.

L-DOPA itself is actively transported into the CNS. There, it is decarboxylated into the important neurotransmitter, dopamine. Dopamine itself cannot cross the blood–brain barrier (BBB). The latter is directly involved in movement and cognition disorders, issues manifested in idiopathic PD. Despite the fact that initial use of L-DOPA, successfully ameliorates some of the symptoms of PD [13], progression of the disease continues. It still remains unclear why that is the case.

The gradual destruction of dopamine-producing neurons in the brain has been clearly implicated in the origin of the disease [14]. At the time symptoms occur, as many as 80% of these neurons have already been destroyed. The cause of their destruction remains to be identified.