Hypothesis: A Role for Quinolinic Acid in the Neuropathology of Glutaric Aciduria Type I

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ABSTRACT: Glutaric aciduria type I is an autosomal recessive metabolic disorder of children associated with severe dystonic motor disturbances and degeneration in the cerebral cortex, striatum and cerebellum. Biochemical studies demonstrate a deficiency in the enzyme glutaryl-CoA dehydrogenase. This enzyme metabolizes substrate derived from dietary tryptophan that could otherwise be converted to quinolinic acid within the brain. The law of mass action predicts that the production of quinolinic acid should be increased in glutaric aciduria type I. Quinolinic acid is a potent neurotoxin and convulsant when it is injected into the central nervous system of experimental animals. This paper argues that quinolinic acid may accumulate within the brain and cause the neuropathology of glutaric aciduria type I.

RÉSUMÉ: Hypothèse: rôle de l'acide quinolinique dans la neuropathologie de l'acidurie glutarique de type I. L'acidurie glutarique de type I est une maladie métabolique autosomale récessive de l'enfance associée à des troubles moteurs sévères de nature dystonique et à une dégénérescence du cortex cérébral, du striatum et du cervelet. Les études biochimiques montrent une déficience en glutaryl-CoA-déshydrogénase. Cet enzyme métabolise un substrat qui provient du tryptophane alimentaire qui, le cas échéant, pourrait être converti en acide quinolinique dans le cerveau. La loi d'action de masse prédit que la production d'acide quinolinique devrait être accrue dans l'acidurie glutarique de type I. L'acide quinolinique est une neurotoxine et un agent convulsivant puissant quand il est injecté dans le système nerveux central d'animaux de laboratoire. Dans cet article, nous discutons de la possibilité que l'acide quinolinique, en s'accumulant dans le cerveau, cause les manifestations neuropathologiques observées dans l'acidurie glutarique de type I.

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Glutaric aciduria type I (GA-I) is one of a number of neurodegenerative dystonic and dyskinetic disorders[1] of children and one of a number of acyl-CoA dehydrogenation deficiencies.[2] It was first described by Goodman and co-workers in the United States in 1975[3,4] and has since been recognized in Denmark,[5,6] Sweden,[7] Canada[8] and France.[9] This disease is difficult to treat effectively and may be fatal.

Children suffering from GA-I are born from a normal pregnancy and pass through the usual milestones of neurological development for the first few months of life.[1-9] Then, patients develop combinations of hypertonicity, spasticity, loss of righting reflexes, convulsions and periods of hypotonicity, particularly during sleep. Over subsequent months these symptoms increase in severity and patients develop dystonia, chorea, athetosis, facial grimacing, cerebellar ataxia, visuomotor apraxia and speech dysarthria. Intellectual development may be normal.[5-7] In one case that came to autopsy after seven years of symptoms, microscopic examination revealed nerve cell loss, gliosis, edema and ischemic damage in the cerebral cortex, putamen and lateral margins of the caudate nucleus; slight atrophy of the cerebellar cortex was also noted, but the globus pallidus, thalamus and brainstem were "largely intact".[10]

The Metabolic Lesion of Glutaric Aciduria Type I

Studies of liver mitochondria, lymphocytes and cultured skin fibroblasts have established that patients with GA-I are severely deficient in the enzyme glutaryl-CoA dehydrogenase (Figure 1) and perhaps also glutaconyl-CoA decarboxylase (see legend to Figure 1).[3-6,9-12] Consequently, patients excrete increased amounts of 3-hydroxyglutaric acid, glutaconic acid, glutarylglycine and particularly glutaric acid. Parents and siblings may also show this enzymatic defect, although to a lesser degree.[4] Given that this enzymatic deficiency is the only clearly identified primary lesion in GA-I, it is likely that its metabolic consequences are involved in the neuropathology of GA-I.

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Hypothesis: Quinolinic Acid Formation is increased in Glutaric Aciduria Type I and is involved in the neuropathology.

Glutaryl-CoA is derived from dietary tryptophan via the "kynurenine" pathway which synthesizes 2-amino-3-carboxymuconic semialdehyde (ACMS). In turn ACMS is converted enzymatically to glutaryl-CoA which may then be metabolized to CO_2 and water by the Krebs citric acid cycle (Figure 1). The "kynurenine" and "glutaryl-CoA" pathways represent the major route for systemic tryptophan metabolism in man. Between 25 to 99% of dietary tryptophan or oral tryptophan loads are metabolized by the kynurenine pathway and up to 25% is excreted as CO_2 and water.[13,14] The deficiency in glutaryl-CoA dehydrogenase in GA-I should decrease the rate of ACMS conversion to glutaryl-CoA, if the synthesis of glutaric acid and other glutaryl-CoA derived organic acids do not increase sufficiently to compensate. Therefore, ACMS should tend to accumulate in GA-I.

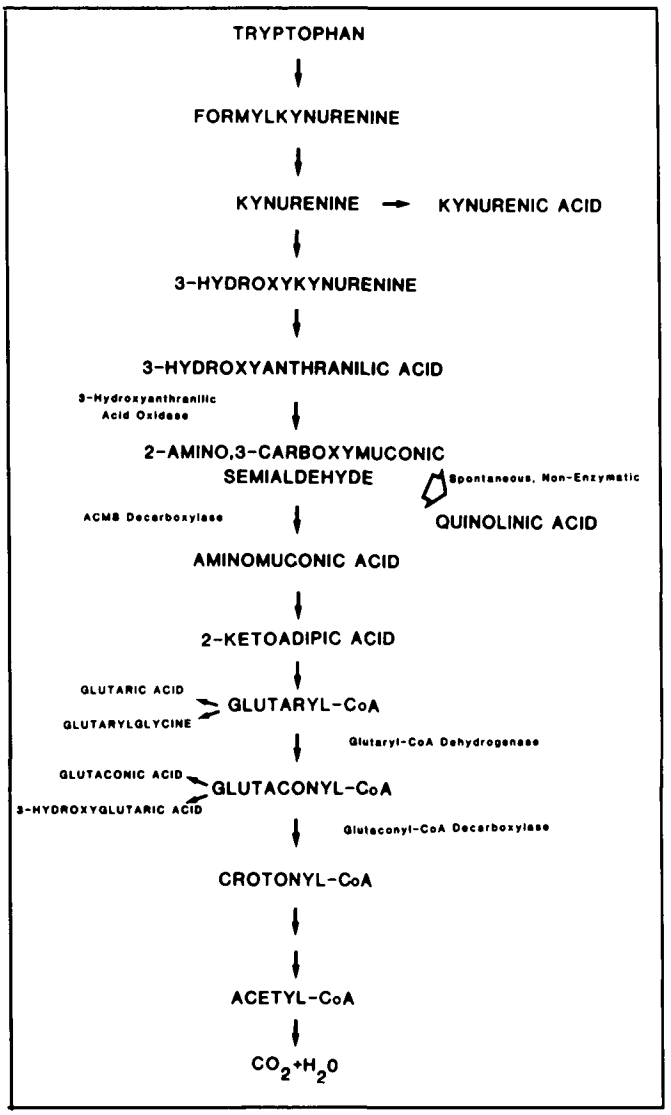

Figure 1 — Metabolism of tryptophan through the kynurenine, glutaryl-CoA and quinolinic acid pathways in man. Patients with GA-I are deficient in glutaryl-CoA dehydrogenase, causing a marked increase in the excretion of glutaric acid. Some assays for glutaryl-CoA dehydrogenase also measure glutaconyl-CoA decarboxylase activity and so glutaconyl-CoA decarboxylase may also be deficient in GA-I (see Ref. 2). The enzyme deficiencies in GA-I may divert substrate away from the glutaryl-CoA pathway (open arrow) and increase the formation of quinolinic acid in the brain which in turn may cause the neurodegeneration, motor disturbances and convulsions of this childhood disease.

An alternate route for ACMS exists. ACMS undergoes a spontaneous, nonenzymatic cyclation reaction to form quinolinic acid (Figure 1). Therefore, an increase in the rate of ACMS formation or concentration should increase the rate of quinolinic acid synthesis in GA-I.

In 1983, Schwarcz and co-workers demonstrated that quinolinic acid was a potent neurotoxin when it was injected directly into the central nervous system of experimental animals.[15] Quinolinic acid also induced clonic-tonic movements of forelimb when it was injected into the striatum and caused contralateral rotation when it was injected into the substantia nigra.[15] Recent studies have established that quinolinic acid is present throughout human and rat brain.[16] McGeer and Singh have shown that neurons are so sensitive to the neurotoxic effect of quinolinic acid that even endogenous quinolinic acid concentrations may be toxic.[17] Quinolinic acid, and other compounds in the kynurenine pathway are also strong convulsants when injected into the brain.[18] If the production of quinolinic acid is increased within the brains of patients with GA-I (see Discussion), then quinolinic acid may be involved in the neuropathology of GA-I.

Discussion

This hypothesis predicts that the enzyme deficiency in the glutaryl-CoA pathway of patients with GA-I causes an increased rate of quinolinic acid production in both systemic and intracerebral tissues and that quinolinic acid accumulates within the brain. The metabolism of tryptophan through the kynurenine, glutaryl-CoA and quinolinic acid pathways has not yet been studied in patients with GA-I. However, there are observations consistent with these predictions.

In rats, substrate flux through the glutaryl-CoA pathway can be reduced by the inhibition of ACMS decarboxylase by pyrazinamide. This drug decreases the systemic synthesis of $^{14}CO_2$ derived from [^{14}C]-L-tryptophan and causes an increase in the excretion of [^{14}C]-quinolinic acid in the urine.[19] For the brain quinolinic acid content to be increased by inhibition of the glutaryl-CoA pathway, increased amounts of quinolinic acid must be synthesized within the brain, because quinolinic acid is not readily permeable across the blood-brain barrier.[20] (The permeability of quinolinic acid into the immature brain is not known). The brain is able to synthesize kynurenine from tryptophan and take up both tryptophan and kynurenine from the blood.[21] The brain also contains the other substrates of the kynurenine pathway[21] and increases its quinolinic acid content following a systemic injection of tryptophan.[22] These observations indicate that the kynurenine pathway is present in the brain and that the brain quinolinic acid content is sensitive to the availability of tryptophan. Given the magnitude of tryptophan metabolism through the glutaryl-CoA pathway, the availability of quinolinic acid precursors should be increased in patients with GA-I and consequently brain quinolinic acid should be increased. In support of this hypothesis M.P. Heyes and S.P. Markey (unpublished observations) have observed a five fold increase in cortical quinolinic acid content following a systemic tryptophan load. Importantly, when the rats were pretreated with pyrazinamide, the same tryptophan load increased the cortical quinolinic acid content over ten fold.

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If quinolinic acid is involved in the neuropathology of GA-I, strategies to reduce brain quinolinic acid concentrations may be useful. One obvious approach would be to reduce the dietary intake of tryptophan. This approach has been used with limited success.[23] However, Moroni and co-workers have reported in a recent abstract[24] that in rats dietary restriction of tryptophan intake produced a paradoxical increase in brain quinolinic acid content. If this response occurs in humans, such a therapy would be contra-indicated. An alternative method, could be to inhibit enzymes of the kynurenine pathway. 3-hydroxyanthranilic acid oxidase is inhibited by 4-chloro-3-hydroxyanthranilic acid, an *in vivo* derivative of 6-chlorotryptophan.[25] In rats, 6-chlorotryptophan can reduce quinolinic acid formation in the liver.[26] The effects of 6-chlorotryptophan on brain quinolinic acid metabolism are unknown, but are currently under study. Quinolinic acid neurotoxicity is mediated via activation of NMDA-type excitatory amino acid receptors.[27] Antagonists of these receptors, including the endogenously synthesized kynurenic acid,[27] are also of potential therapeutic benefit.

Conclusions

Collectively the studies of systemic and brain tryptophan metabolism indicate that the brain content of quinolinic acid may be increased in patients suffering from GA-I. Therefore, quinolinic acid may be a crucial etiological factor in the neuropathology of GA-I. This hypothesis is directly testable and patients are currently being recruited for study. Blockade of ACMS decarboxylase by pyrazinamide may provide an animal model for GA-I. If the hypothesis is then supported strategies to decrease the cerebral content of quinolinic acid or blockade of quinolinic acid receptors may offer a new approach to therapy in GA-I.

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