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Argininosuccinic Aciduria and Maple Syrup Urine Disease

By C. E. Dent

We described two years ago our preliminary investigations on a new, presumed inborn, error of amino acid metabolism affecting two sibs in a family of 5 children (*Allan*, *Cusworth*, *Dent* and *Wilson:* Lancet **1958**/I, 182). The two sibs were grossly mentally retarded, but otherwise enjoyed good health. They each showed large excretions of a complex amino acid that we were then unable to identify. *Westall*, in our laboratory, has now shown that the unknown metabolite is argininosuccinic acid (ASA) (*Westall:* Biochem. J. **77**, 135 [1960]) and that the sibs each excrete daily nearly 3 g in their urine. Fortunately for us the biochemists (*Ratner:* Advanc. Enzymol. **15**, 356 [1954]) have recently shown that ASA is a normal intermediate in the urea cycle (Fig. 1). It remains for us to think further as to the mechanism of the disease process and as to its possible treatment.

The most puzzling feature of the disease, which we now suggest should be named argininosuccinic aciduria, is that urea levels in blood and urine are normal. One would expect that a metabolic block leading to the accumulation and excretion of 3 g daily of ASA would lead to a profound disorder of urea formation. Our current hypothesis is that an enzymic deficiency in ASA splitting enzyme (ASA-ase) is the immediate cause of the disease but that for some reason it involves a metabolic sequence mainly concerned in brain metabolism and not for urea formation by the liver. In favour of this is the finding of higher concentrations of ASA in the cerebrospinal fluid than in the plasma. The block in the brain could deal with arginine synthesis or with the formation of some other type of compound such as a pyrimidine derivative for which ASA is believed to be an intermediate (*Dent:* Proc. roy. Soc. Med. **52**, 885 [1959]).

In case deficiencies of these compounds could cause the disease, we have given orotic acid (a pyrimidine) but found no acute changes in behaviour nor in the abnormal EEG tracings. We have also given

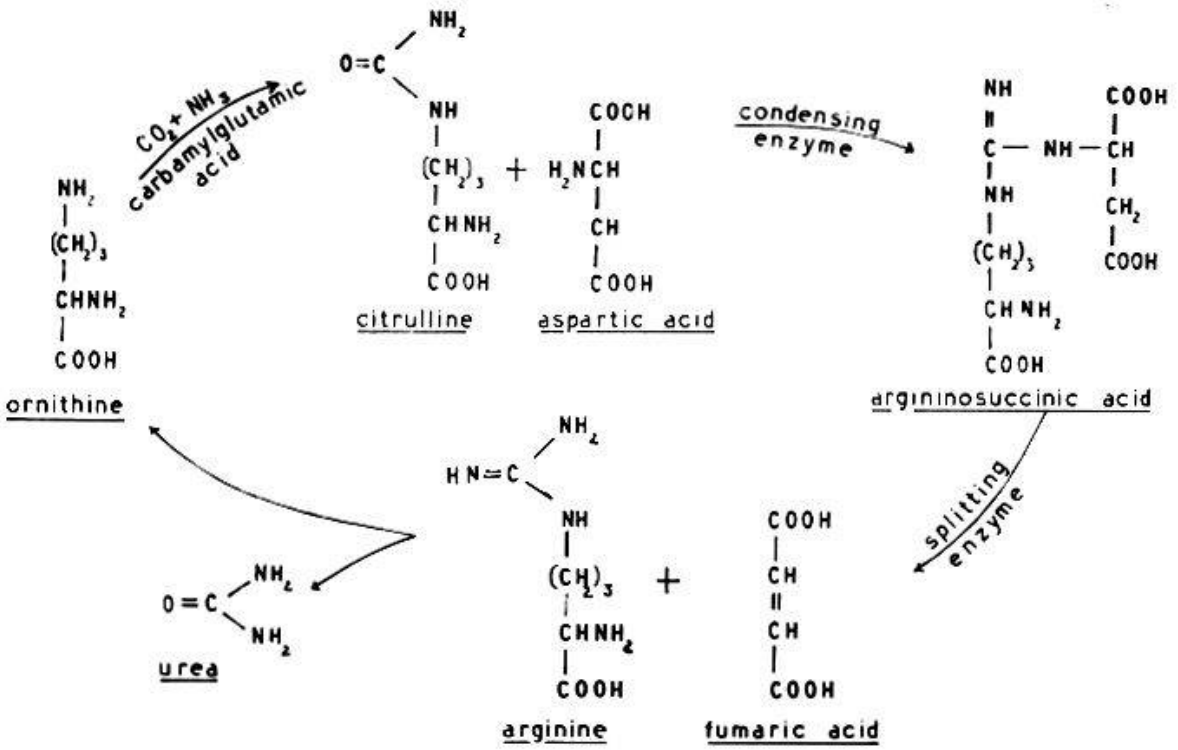
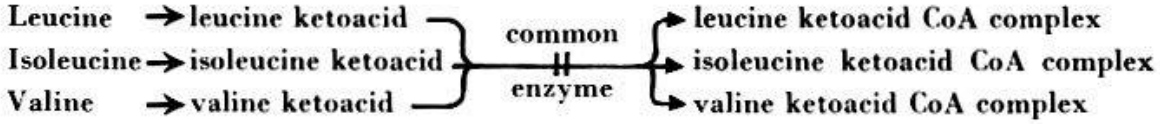


Fig. 1.

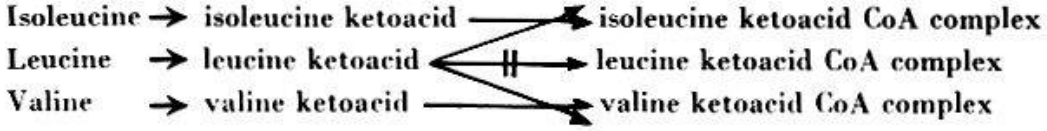
arginine by mouth and by vein with similar disappointing results. As a sideline to the latter we found (with help from Dr. *D. Smeenk*) that intravenous arginine induced a temporary gross cystine lysine ornithinuria owing to a blocking of the renal tubular mechanism common to these four amino acids. The arginine worked better than the intravenous lysine we have previously used in a similar study (*Robson* and *Rose:* Clin. Sci. **16,** 75 [1957]) which is not too surprising as arginine is more readily reabsorbed by the renal tubule than lysine.

Maple Syrup Urine Disease, that very serious hereditary form of progressive cerebral degeneration, described first by *Menkes*, *Hurst* and *Craig* (Pediatrics **14,** 462 [1954]) did not have a firm biochemical basis till *Westall*, *Dancis* and *Miller* (Amer. J. Dis. Child. **94,** 571 [1957]) discovered that the plasma and urine contained large quantities of the branch chain amino acids (leucine, isoleucine and valine) and later (as did others elsewhere) of their corresponding keto acids. It is of especial interest here to comment that the obvious suggestion of a site of the metabolic block is at the keto acid stage when it has to link first with Coenzyme A in the first stage of oxidative dicarboxylation and before further breakdown is possible. We like to think that such inborn errors of metabolism should involve one enzyme system only and one substrate only. How then is it that the three branch chain amino acids are involved together? There seem to be two possibilities if only one enzyme is to be involved. The first is that the enzyme is not very specific and can there-

fore handle all three compounds i. e. the metabolic block would be shown thus at the stage marked "common enzyme":–



The second possibility is that 3 enzymes are normally concerned, one for each branch chain amino acid, and that one only is missing or malfunctioning in the disease, say that for leucine keto acid. The immediate result of the metabolic block would be accumulation of leucine itself and of the keto acid derived from it. The large accumulations of these compounds could then, however, block the isoleucine and valine mechanisms by a competition mechanism owing to the general molecular resemblance between them. This could be shown as follows:–



The true block occurs only between leucine keto acid and leucine keto acid CoA complex, but this could induce a block for the other two keto acids. A similar situation occurs in phenylketonuria when blocks in tryptophan metabolism are well known to occur secondary to the phenylalanine accumulations.

We had suspicions in Maple Syrup Urine Disease that the primary block could involve leucine only for analysis showed that most of the keto acid accumulation involves the leucine derivative. These speculations are not empty ones. If a diet is to be devised to correct the abnormality of plasma levels, the diet will have to be made deficient in all three branch chain amino acids if the first mechanism is concerned while, if it follows the second mechanism, the diet will have to be deficient in only the one amino acid concerned.

Unpublished work will be described along these lines (*Dent* and *Westall:* Arch. Dis. Childh., in press). Diets have been devised low in branch chain amino acids, using gelatine and casein hydrolysate as main source of amino acid intake. Plasma and urine analyses have been done on the diets alone and after they had been supplemented by each of the branch chain amino acids in turn. The results showed that it was possible to make normal the plasma amino acid levels by dietary means. Furthermore, each amino acid showed an individual block in metabolism at the

keto acid stage thus favouring the first "common enzyme" mechanism shown above.

The baby under investigation progressed well physically and did not deteriorate mentally while more normal plasma amino acid levels were being induced on the various diets. Unfortunately, it died soon after being put on a normal diet and while we were awaiting arrival of a large consignment of pure amino acids for a further longer term dietary trial.

Summary

Further studies of the enzymic disorder in argininosuccinic aciduria lead us to underline the fact that there is no gross disorder in the Krebs urea cycle. Probably there is a deficiency of ASA-ase limited to the brain and involving a different metabolic sequence than that of urea production. Attempts to treat the disease on this basis have, however, failed up to now.

In maple syrup urine disease it is possible to make normal all the metabolic abnormalities by providing a diet sufficiently low in leucine, iso-leucine and valine. While on this diet, it is possible to show that the child cannot metabolise either of these three amino acids fed separately. We presume there is a common enzyme, missing in the disease, responsible for the metabolism of the three corresponding keto acids.

Zusammenfassung

Weitere Studien der Enzymstörung bei der Argininosuccinicacidurie führen uns dazu, die Tatsache zu unterstreichen, daß keine wesentliche Störung im Krebs'schen Harnstoffzyklus besteht. Vielleicht besteht ein Mangel an Succinoargininase, der auf das Gehirn beschränkt ist; dieses beim gesunden Kind vorhandene Ferment greift in einen von der Harnstoffsynthese verschiedenen Stoffwechselvorgang ein. Versuche, die Krankheit auf dieser Grundlage zu behandeln, haben bis zum jetzigen Zeitpunkt fehlgeschlagen.

Bei der Ahorn-Sirupurin-Krankheit ist es möglich, alle Stoffwechselabnormitäten zu normalisieren, wenn man eine Diät verabreicht, die genügend arm an Leucin, Isoleucin und Valin ist. Während dieser Diät ist es möglich zu zeigen, daß das Kind keine von diesen drei Aminosäuren abbauen kann, wenn man sie einzeln verfüttert. Wir vermuten, daß es ein gemeinsames Enzym gibt, das bei der Krankheit fehlt und verantwortlich ist für den Stoffwechsel der drei entsprechenden Ketosäuren.

Résumé

Des études complémentaires du désordre enzymatique, dans l'acidurie arginino-succinique, nous ont permis de mettre en évidence le fait qu'il n'y a pas de trouble important dans le cycle de l'urée selon Krebs. Il est probable qu'il y ait une insuffisance de ASA-ase, limitée à la matière cérébrale; il s'agit probablement d'un enzyme qui est normalement lié à un développement métabolique, différent de la synthèse d'urée. Les tentatives qui ont été faites, de traiter cette maladie sur la base de cette hypothèse n'ont toutefois donné aucun résultat jusqu'à présent.

Dans l'affection avec une urine à odeur de sirop d'érable il est possible de corriger tous les troubles métaboliques, en donnant une nourriture suffisamment pauvre en leucine, isoleucine et valine. Sous l'effet de cette diète, on peut démontrer que l'enfant est incapable de métaboliser l'un de ces trois amino-acides administrés séparément. Cela permet de supposer qu'il manque dans cette maladie un enzyme commun, qui soit capable de métaboliser les trois kétoacides correspondants.

Riassunto

Studi successivi sul disordine enzimatico nell'aciduria arginino-succinica ci condussero a sottolineare il fatto che non esiste un'alterazione grave nel ciclo dell'urea di Krebs. Probabilmente esiste una mancanza di ASA-asi limitata al cervello; e che provoca normalmente uno sviluppo metabolico diverso da quello che conduce alla produzione di urea. Tentativi di curare questa malattia su tale base sono però fino ad oggi falliti.

Nella malattia cosiddetta da «urina simile a sciroppo d'acero» è possibile normalizzare tutti i difetti metabolici somministrando una dieta povera di leucina, isoleucina e valina. Durante questa dieta è possibile mostrare che il bambino non può metabolizzare alcuno di questi tre aminoacidi somministrati separatamente. Riteniamo che alla base del metabolismo dei tre chetoacidi corrispondenti sia un enzima comune che manca nella malattia.