# Saccharopinuria : a New Inborn Error of Lysine Metabolism

DURING the routine screening of mentally retarded persons in Northern Ireland for amino-acid disorders with the aid of paper chromatographic techniques, a patient was discovered who excreted large quantities of lysine, citrulline, histidine and an unidentified amino-acid in her urine.

The patient was a girl aged 22, whose performance in a full-scale WAIS intelligence test was recorded as 67. Apart from her small stature, 4 ft. 9 in., there was nothing of note in her general appearance. No history of fits was elicited but she had an abnormal electroencephalograph. There are six half siblings in the family (the father of the propositus is not known). Her siblings and her mother are of normal intelligence and show normal amino-acid excretion patterns.

Further investigation of the patient's urine with an ion exchange quantitative amino-acid analyser confirmed that lysine and citrulline were present in large concentration, and that what was thought to be a large quantity of histidine on the paper chromatogram was actually made up of homocitrulline and histidine. Homoarginine and aminoadipic acid were also found to be present.

An examination of the literature with particular reference to studies of lysine biosynthetic pathways suggested that the unidentified amino-acid might be saccharopine[1]. Identification of the patient's unknown amino-acid component as saccharopine was made possible by a gift of the pure substance from Dr Darling (Denmark).

When the pure substance was added to the patient's urine and analysed on the ion exchange column, the original unidentified peak was intensified. It is also noteworthy that the unknown urinary component and pure saccharopine both give ninhydrin derivatives which show uniquely high light absorption at 440 mμ in comparison with other α-amino-acids. Further evidence of identity was the superimposition of saccharopine and the unknown spot when the urine was examined by paper chromatography in two other different solvent systems.

In the serum, saccharopine and homocitrulline were present in small quantities. The concentration of lysine was increased to 4–5 times the normal level and that of citrulline was similarly raised. The unknown compound, identified here as saccharopine, also appeared in high concentration in the cerebrospinal fluid.

Fig. 1 indicates the possible routes of lysine degradation in man. It is thought that the pathway through pipecolic acid and aminoadipic acid is the main pathway[2].

Recent work with neurospora, yeasts and animals has suggested alternative routes for lysine metabolism in man. Observations in patients with hyperlysinaemia have shown two of these pathways to function in man but to be of minor importance only. Thus homocitrulline and homoarginine were demonstrated in increased quantities in the urine of adults given a lysine load[3] and both have been reported in the urine of hyperlysinaemic patients[4–6]. ε-*N*-Acetyl-L-lysine was suggested to be the first step in lysine metabolism by Paik and Kim[7], and was found to be present in patients with hyperlysinaemia and in healthy individuals after a lysine load[5,6]. The pathways given here, however, only account for a small quantity of ingested lysine.

Saccharopine was first isolated from brewers' yeast[1] and has been shown[8] to be a precursor of lysine in yeast. There is evidence[9] that the first step of lysine degradation by rat liver mitochondrial preparations is a reaction with α-ketoglutaric acid to produce saccharopine (*N*(L-glutaryl-2-L-lysine)). If this is so, it would seem that the suggestion[2] that pipecolic acid is on the chief degradative pathway is incorrect.

Perhaps even more striking than the discovery of the excretion of saccharopine is the finding of excess citrulline in this patient.

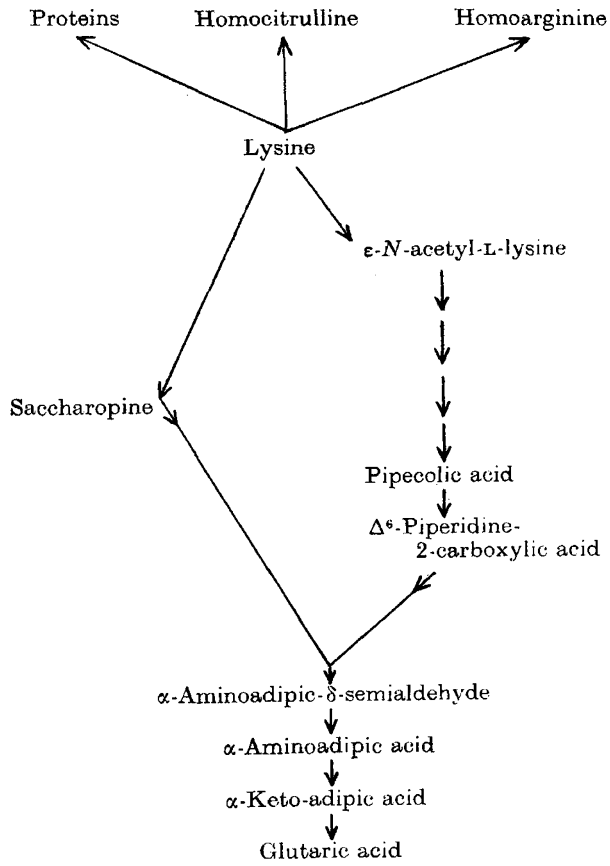


Fig. 1. Schematic summary of known lysine pathways.

It is interesting in this connexion that work by Borsook (as stated by Meister[10]) suggested that lysine nitrogen is used to some extent for the formation of citrulline and arginine. Also it has been noted[7] that the enzyme responsible for the synthesis of ε-*N*-acetyl-L-lysine reacts with L-ornithine better than with lysine and suggests the possibility that ε-lysine acylase may be identical with ornithine transcarbamylase. Certainly in this newly discovered disorder there appears to be some connexion between lysine and citrulline metabolism.

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