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Developmental changes and polymorphism in human alcohol dehydrogenase.
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SUMMARY

1. Human alcohol dehydrogenase (ADH) has been investigated by spectrophotometry assay and by starch-gel electrophoresis.

2. Assays were carried out at pH 8-8 and pH 11-0 on liver samples obtained *post mortem* from 129 adults over the age of 20, 37 premature infants and infants less than one year old and 56 foetuses. Sixteen cases of the previously described atypical pH ratio phenotype were identified among the 166 adults and infants tested. No examples of the atypical pH ratio phenotype were encountered among the foetuses. On average the foetal liver ADH activity was less than in adults and it appeared to increase with increasing gestational age.

3. Electrophoretic analyses of ADH in liver samples obtained from 117 foetuses of various gestational ages, 62 premature infants and infants less than a year old and a group of more than 200 adults over the age of 20, indicate that developmental changes occur during intrauterine life.

4. The atypical pH ratio phenotype liver ADH isozyme pattern was found to be electro-phoretically different from that of the usual pH ratio phenotype.

5. The ADH isozyme pattern in lung tissue was the same in adults, infants and foetuses. The overall activity was low and mainly concentrated in a single isozyme which was electrophoretic-ally indistinguishable from the main ADH isozyme of adult liver. Usual and atypical pH ratio phenotypes were identified, both by assay and by starch-gel electrophoresis, in foetal, infant and adult lung specimens.

6. The ADH activity of kidney and intestine was too weak for assay with ethanol as substrate. In adults the isozyme patterns in kidney were similar to those found in adult liver. In foetal intestine and kidney, however, the ADH isozymes were quite different from those of adult liver and also foetal liver. Three distinct phenotypes, designated ADH_3 1, ADH_3 2-1 and ADH_3 2, were recognized in foetal kidney and intestine, occurring with frequencies of 0–42, 0–42, and 0–16 respectively in a survey of 117 specimens.

7. The appearance of the ADH isozyme patterns in liver and in foetal kidney and intestine is consistent with the hypothesis that ADH has a dimeric sub unit structure.

8. The findings suggest that at least three autosomal gene loci may be concerned in determining the structure of alcohol dehydrogenase in man.

(a) Locus ADH_1primarily active in the liver in early foetal life, becoming less active during gestation and only weakly active during adult life.
(b) Locus ADH_2 (i) expressed in lung in early foetal life and remaining active in this tissue throughout life, (ii) active in liver after about the first trimester and gradually becoming more active so that in adults this locus is responsible for most of the liver ADH activity, (iii) also active in adult kidney, (iv) the atypical pH ratio phenotype is probably determined by a variant allele at the ADH_2 locus.
(c) Locus ADH_3- active during foetal and early post-natal life in intestine and kidney. The variant phenotypes ADH_3 1, ADH_3 2-1 and ADH_3 2 are thought to represent the genotypes $ADH_1{}^3ADH_3{}^1$,$ADH_3{}^2ADH_3{}^2$ and $ADE_3{}^1ADH_3{}^2$ respectively, where $ADH_3{}^1$ and $ADH_3{}^2$ are alleles at the ADH_3 locus. The gene-frequency estimate of $ADH_3{}^1$ is 0.63 and of $ADH_3{}^2$ is 0.37.