E₁^k, another quantitative variant at cholinesterase locus 1

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SUMMARY Two families segregating for the atypical (E₁^a) allele at cholinesterase locus 1 are described. Unusual results for dibucaine inhibition led to the recognition of a new allele (E₁^k) also segregating in these families. The enzymatic and immunological data are consistent with the hypothesis that E₁^k causes reduction of 'usual' (E₁^u) molecules by about 33%. Whether the reduction of E₁^u caused by E₁^k is caused by retarded synthesis or accelerated degradation of serum cholinesterase remains to be determined.

Several quantitative variants at serum cholinesterase (E.C.3.1.1.8) locus 1 have been described. These result in lowered serum cholinesterase activity and, when interacting with the E₁^a (atypical) allele, give dibucaine inhibitions below those of E₁^uE₁^u heterozygotes. Interaction with E₁^a led to the discovery of the E₁^s (Liddell et al., 1962) and E₁^i (Garry et al., 1976) variants. E₁^s exists in several forms (Rubinstein et al., 1970) and results in 95 to 100% diminution of E₁^u molecules; E₁^i results in about 66% reduction. One family has been described in which several members have greatly increased amounts of apparently normal serum cholinesterase (Neitlich, 1966; Yoshiada and Motulsky, 1969). The gene responsible has been named E Cynthia but it is not yet known if it is active at cholinesterase locus 1 or locus 2.

We present here two families with a quantitative variant at cholinesterase locus 1 which results in about 33% reduction of E₁^u molecules; both of these families were recognised by means of interaction with the E₁^a gene.

Methods

The enzymatic and immunological methods used were the same as given in earlier publications (Garry et al., 1976; Rubinstein et al., 1976; Dietz et al., 1973). (Table II in Garry et al. (1976) gives the cholinesterase activities and inhibitions of the known phenotypes as determined in our laboratory.)

Results

S. FAMILY

The index case (II.1) was discovered by means of prolonged apnoea after administration of succinylcholine. The cholinesterase activities and inhibitions of the sera of the family members are given in the Table. Two individuals (III.2 and III.3) have dibucaine inhibitions in a range not previously found. This family can be explained by assuming segregation for a new allele¹ which must have entered the family through II.2 who is considered to be genotype E₁^uE₁^k.

¹Termed E₁^a in honour of Dr Werner Kalow who clarified the recognition and inheritance of the E₁^a allele by means of dibucaine inhibition.

| Family | Pedigree No. | Presumed genotype | Cholinesterase activity | Inhibition, % | Dibucaine | Fluoride |
|--------|--------------|-------------------|-------------------------|--------------|----------|---------|
| S.     | I.1          | E₁^uE₁^s           | 5.62                    | 74-3         | 81-2     |         |
|        | II.1         | E₁^uE₁^s           | 1.35                    | 18-5         | 83-6     |         |
|        | 2            | E₁^uE₁^s           | 6.74                    | 83-4         | 77-7     |         |
|        | 3            | E₁^uE₁^s           | 4.81                    | 76-8         | 82-5     |         |
|        | 4            | E₁^uE₁^s           | 1.29                    | 14-8         | 82-2     |         |
|        | III.1        | E₁^uE₁^s           | 8.97                    | 84-5         | 79-3     |         |
|        | 2            | E₁^uE₁^s           | 2.21                    | 60-0         | 81-9     |         |
|        | 3            | E₁^uE₁^s           | 2.67                    | 65-3         | 78-2     |         |
|        | 4            | E₁^uE₁^s           | 8.09                    | 84-4         | 81-3     |         |
|        | 5            | E₁^uE₁^s           | 6.91                    | 75-5         | 79-4     |         |
| IV.1   | E₁^uE₁^s     | 8.72               | 74-5                    | 79-8         |         |         |
| 2      | E₁^uE₁^s     | 9.38               | 84-6                    | 79-5         |         |         |
| 3      | E₁^uE₁^s     | 8.60               | 83-8                    | 82-1         |         |         |
|        | J.           | II.1               | E₁^uE₁^s                | 2.97         | 63-1     | 79-7    |
|        | 2            | E₁^uE₁^s           | 2.10                    | 10-5         | 80-0     |         |
|        | 4            | E₁^uE₁^s           | 5.26                    | 85-5         | 80-4     |         |
|        | 5            | E₁^uE₁^s           | 6.78                    | 74-2         | 85-2     |         |
|        | III.1        | E₁^uE₁^s           | 5.53                    | 75-8         | 78-0     |         |
|        | 2            | E₁^uE₁^s           | 3.28                    | 66-0         | 79-0     |         |
|        | 3            | E₁^uE₁^s           | 7.76                    | 82-2         | 80-3     |         |
|        | 4            | E₁^uE₁^s           | 8.49                    | 82-7         | 81-5     |         |

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Subjects IV.2 and IV.3 must also be $E_i^aE_i^k$. Subjects III.2 and III.3 are assigned genotype $E_i^aE_i^k$. The pedigree and most likely genotypes are given in Fig. 1. Though I.2 may have been $E_i^aE_i^1$ (in which case II.1 and II.4 would be $E_i^aE_i^1$), the fact that II.1, II.3, II.4, III.2, III.3, and III.5 all have at least one $E_i^a$ gene suggests that I.2 was probably $E_i^aE_i^1$ (or, more remotely, $E_i^aE_i^a$ or $E_i^aE_i^k$).

J. FAMILY

The index case (II.2) was also discovered by prolonged apnoea after succinylcholine. The data on family members are given in the Table. Two individuals, II.1 and III.2, have dibucaine inhibitions unlike those found in known phenotypes but similar to those of III.2 and III.3 in the S. family. Assuming the same explanation as that given for the S. family, II.1 and III.2 are assigned genotype $E_i^aE_i^k$. Either I.1 or I.2 must have been $E_i^aE_i^1$; the other could have been $E_i^aE_i^k$ or $E_i^kE_i^k$. Since the $E_i^a$ gene is more frequent than the $E_i^k$ gene, $E_i^aE_i^k$ is more likely; that is why II.2 is assigned $E_i^aE_i^k$ rather than $E_i^kE_i^k$. (Very remotely, I.1 could have been $E_i^aE_i^a$ and I.2 $E_i^aE_i^k$.) II.4 would then be $E_i^aE_i^k$. Against this is the cholinesterase activity of 5-26 found in II.4 as $E_i^aE_i^k$ would be expected to give a very much lower value.) II.4 is, therefore, classified as $E_i^aE_i^k$. The most probable genotypes are given along with the pedigree in Fig. 2.

Figure 3 clarifies the identification of $E_i^aE_i^k$ with respect to previously known genotypes in terms of dibucaine and fluoride inhibitions. The $E_i^aE_i^k$ area falls just between those for $E_i^aE_i^1$ and $E_i^kE_i^k$. $E_i^aE_i^k$ cannot be distinguished from $E_i^aE_i^a$, $E_i^aE_i^s$, or $E_i^aE_i^1$ by inhibitions.

Following the reasoning used for $E_i^1$ (Garry et al., 1976), the $E_i^k$ allele can be explained as resulting in reduced numbers of circulating $E_i^u$ molecules whether because of reduced synthesis or accelerated degradation. Fig. 4 (derived from Fig. 4 of Garry et al., 1976) relates dibucaine inhibitions to mixtures of $E_i^a$ and $E_i^k$ molecules in various proportions. The average dibucaine inhibition of the four $E_i^aE_i^k$ subjects from the two families given above indicates that the ratio of $E_i^u$ to $E_i^a$ molecules in their sera is about 40:60. This corresponds to an approximate 33% reduction of $E_i^a$ molecules caused by the $E_i^k$ allele. $E_i^k$ causes less reduction of $E_i^u$ molecules than $E_i^1$—33% vs 66%.

The average cholinesterase activity of $E_i^aE_i^k$ sera should, therefore, be higher than that of $E_i^aE_i^1$ sera. This is what is observed, 2.78 vs 1.93.

The relative diminution of $E_i^u$ molecules in the serum of the two $E_i^aE_i^k$ subjects (II.1 and III.2) in the J. family was also shown immunologically. Fig. (based on Fig. 4 of Rubinstein et al., 1976) relates the...
choolinesterase activity of sera of various genotypes to immunological reactivity by gel immunodiffusion. The two $E_1^aE_1^k$ sera are found in an area of the plot distinct from $E_1^aE_1^a$, $E_1^aE_1^k$, and $E_1^aE_1^a$ sera and close to that of $E_1^aE_1^1$ sera.

**Discussion**

The recognition of $E_1^k$ in the two pedigrees given here is based on interaction of $E_1^a$ with the resultant production of dibucaine inhibition unlike any found hitherto—precisely the way in which $E_1^j$ was also found (Garry et al., 1976). Inspection of Fig. 3 and 4 shows that other quantitative variants may well be discovered in the same way. Dibucaine inhibitions falling between 30 to 50%, if segregating appropriately, would indicate quantitative variants intermediate in their effects between $E_1^a$ and $E_1^j$. Such variants, if they exist, should account for roughly 75 to 90% reduction of $E_1^a$ molecules.

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