Genetic Influence upon Phenobarbital-induced Increase in Rat Liver Supernatant Aldehyde Dehydrogenase Activity*

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SUMMARY

Treatment with phenobarbital of rats which are genetically selected results in a greater than 10-fold increase in nicotinamide-adenine dinucleotide (NAD)-dependent aldehyde dehydrogenase present in the supernatant but not the mitochondrial fraction of liver. This effect represents one of only a few known cases where intrastrain differences in a drug-induced increase in enzyme activity is genetically controlled.

The kinetic characteristics of the enzyme from phenobarbital-treated rats are the same, regardless of whether or not the enzyme activity in the liver is increased.

It is also demonstrated that rat liver supernatant contains a second NAD-dependent aldehyde dehydrogenase which (a) is resistant to induction by phenobarbital; (b) oxidizes p-carboxybenzaldehyde; (c) is relatively uninhibited by disulfiram; (d) has a heat stability different from the inducible enzyme.

It has been found recently that the administration of phenobarbital to rats results in a 10-fold increase in NAD-linked aldehyde dehydrogenase in the supernatant fraction of the liver. This response is dependent upon the genotype of the animal and is due to the presence of a single autosomal co-dominant gene (2). Numerous examples of genetically controlled differences in enzyme levels are known (3). Likewise, the activity of some enzymes (e.g. the microsomal drug-metabolizing system) is increased by administration of various compounds (4). There are few known examples, however, of drug-induced increases in enzyme activity which are dependent upon the genotype of the individual.

Gielen et al. (5) have recently described a microsomal hydroxylase enzyme system that is inducible in genetically selected strains of mice. The effect is inherited as a dominant trait and is demonstrable in a number of tissues besides the liver. The activity of δ-aminolevulinic acid synthetase is increased by barbiturates and this effect is dependent upon the genotype of the animal (6).

The present report further describes the characteristics of the increase in aldehyde dehydrogenase activity brought about by phenobarbital administration and presents evidence that similar enzymes in kidney and brain are unaffected by such treatment. Direct evidence is also presented for the presence of a second liver supernatant aldehyde dehydrogenase, the activity of which is also not altered by phenobarbital administration. Rat liver also contains an aldehyde dehydrogenase in the mitochondria; however, unlike the enzyme found in the supernatant, its activity was found to be unaltered by phenobarbital administration in any group of rats tested (2).

MATERIALS AND METHODS

Materials—All chemicals were of the highest quality available. Volatile aldehydes used as substrates were periodically distilled under nitrogen and stored until use at -20°. Solutions of aldehydes were assayed enzymatically as previously described (7). Phenobarbital for injection (20 mg per ml) was dissolved in NaOAc and adjusted to pH 9 with HCl. Other compounds were dissolved and administered as detailed in the tables.

Animals—Adult rats and mice of both sexes were obtained from commercial sources as noted in the tables. A closed breeding colony of Long-Evans rats is maintained in this laboratory. Animals are designated RR for homozygous reactor animals, rr for homozygous nonreactor animals, and Rr for the heterozygous reactor animals as defined earlier (2). Unless otherwise noted, the quantity of phenobarbital injected intraperitoneally was 100 mg per kg once daily for 3 successive days.

Animals receiving injections of an equal volume of saline had aldehyde dehydrogenase activities no different from those of rats not receiving injections. All controls reported in this report refer to animals not receiving injections. The most convincing "control" is the animal receiving phenobarbital injections, which, because of its genetic constitution, does not demonstrate an increase in aldehyde dehydrogenase activity but does manifest all other observed responses to phenobarbital.

Tissue Preparation and Enzyme Assays—Whole organs were removed immediately after decapitation of the animal.
to perform liver biopsies the animals were anesthetized with ether and tissue samples were obtained through a small abdominal incision.

Subcellular fractionation of various tissues was carried out as previously described (2). Brains were homogenized as a 20% suspension in 0.25 M sucrose and centrifuged at 100,000 × g for 1 hour. The supernatant was decanted and adjusted to 50% saturation with (NH₄)₂SO₄ at 4°C. Merapetothanol was added to this solution to a final concentration of 0.01 M and it was centrifuged at 15,000 × g for 5 min. The resulting precipitate was dissolved in 0.25 M sucrose and centrifuged. The supernatant from this procedure was used for assay of aldehyde dehydrogenase activity. Recovery of aldehyde dehydrogenase activity in the brain supernatant after (NH₄)₂SO₄ precipitation as determined by assay of indoleacetic acid production from indoleacetaldehyde (8), was 86 ± 6.8% SEM.

Aldehyde dehydrogenase activity in all assays was determined by following the net rate of NADH formation spectrophotometrically. Unless otherwise noted 1 mM NAD and 0.33 mM propionaldehyde were employed in each assay sample. Control samples contained no propionaldehyde. Pyrazole (33 μM) was added in the assay of the liver and kidney supernatant enzyme in order to inhibit alcohol dehydrogenase, which interferes with the assay. Alcohol dehydrogenase activity was determined by the net rate of decrease in NADH concentration in the presence of NADH and propionaldehyde, 0.33 mM each (9). Lactate dehydrogenase (10), aniline hydroxylase (11), α-glycerophosphate dehydrogenase (12), and amnonipyrine demethylase (13) were assayed by described methods.

RESULTS

We have shown that the ability of rats to respond to injected phenobarbital by an increase in aldehyde dehydrogenase in the liver supernatant is inherited as an autosomal co-dominant characteristic in a manner described by classic Mendelain genetics (2). The initial studies were carried out using animals with a phenotype determined by the assay of aldehyde dehydrogenase activity in a liver biopsy following phenobarbital treatment. Following the biopsy, the animals were allowed to heal and further experiments were carried out at least 4 weeks later. More recent studies have employed animals of the F₁ through the F₅ generation that were found to breed true for an increase or no change in oxidative activity toward propionaldehyde, but only 19% inhibition of the activity toward p-carboxybenzaldehyde. The presence of this second enzyme activity is essentially constant regardless of the treatment of the animal prior to hepatic transplantation. The use of substrates other than propionaldehyde demonstrated that a second aldehyde dehydrogenase enzyme is present in the liver supernatant of rats treated with phenobarbital (Table I). The rate of NAD-dependent oxidation of p-carboxybenzaldehyde, as well as di-glycolaldehyde, glycolaldehyde, and glyoxylic acid in the liver supernatant is not affected by phenobarbital treatment of the animal. The presence of this second enzyme in the untreated animal is also evident from heat denaturation curves of the enzyme activities employing propionaldehyde and p-carboxybenzaldehyde as substrates (Fig. 1).

Some progress has been made toward purification of the enzyme with activity increased by phenobarbital treatment as illustrated in Table II. It is evident from these data that activities toward propionaldehyde and p-carboxybenzaldehyde behave differently upon fractionation with ammonium sulfate. Also mixed substrate experiments with saturating amounts of propionaldehyde and p-carboxybenzaldehyde show additive or nearly additive rather than competitive rates, again illustrating the presence of two enzyme activities. Disulfiram at a dose of 600 mg per kg administered to phenobarbital-treated animals, 16 hours prior to removal of the liver, resulted in 95.8% inhibition of oxidative activity toward propionaldehyde, but only 19% inhibition of the activity toward p-carboxybenzaldehyde.

Kinetic Characteristics—The apparent Kₘ values for the enzymes, using propionaldehyde and NAD as substrates, are relatively constant regardless of the treatment of the animal prior to examination of the enzyme (Table III). Likewise the Kₘ value for p-carboxybenzaldehyde is unchanged by phenobarbital treatment. Studies of the pH optimum for the enzyme from rats

| Substrate               | Concentration (mM) | phenobarbital treated | Uninjected |
|-------------------------|---------------------|-----------------------|------------|
| Acetaldehyde            | 3.3                 | 412.5                 | 27.3       |
| Propionaldehyde         | 0.33                | 783.4                 | 29.5       |
| p-Methoxybenzaldehyde   | 0.33                | 343.5                 | 25.8       |
| Benzaldehyde            | 0.33                | 819.2                 | 23.7       |
| p-Nitrobenzaldehyde     | 0.33                | 647.4                 | 26.4       |
| Phenylacetalddehyde     | 0.33                | 272.8                 | <5.0       |
| Glycolaldehyde          | 0.33                | 28.6                  | 39.1       |
| Glyoxylic acid          | 0.33                | 74.9                  | 41.5       |
| Glyoxal                 | 0.33                | 2.4                   | 7.2        |
| p-Glycolaldehyde        | 0.33                | 60.3                  | 45.6       |
| p-Carboxybenzaldehyde  | 0.33                | 34.1                  | 45.9       |

* Substrate was dissolved in 10% propylene glycol.
receiving injections or control rats also revealed no differences. The use of acetaldehyde as a substrate is complicated by an apparent substrate activation at concentrations above 0.33 mM. Double reciprocal plots with propionaldehyde also show apparent substrate activation at concentrations above 3.3 mM. Unless otherwise noted, studies reported were carried out with a propionaldehyde concentration of 0.33 mM although the activity at 3.3 mM was also routinely determined in order to detect possible effects evident at high concentrations of propionaldehyde.

Table IV summarizes the results of experiments performed on other strains of rats and several strains of mice treated with phenobarbital in an attempt to increase the liver supernatant aldehyde dehydrogenase activity. The "randomly bred" strains of rats (Sprague-Dawley, Long-Evans, Wistar and Charles-River) include animals of all three groups, RR, Rr, and RR. Inbred strains of rats (Fischer, Buffalo-Lewis, ACIF/MaI and BN/F MaI) are homozygous as expected.

An insufficient number of mice in each strain has been tested to determine whether or not there are nonreacting animals present. However, the maximal stimulation achieved in these experiments was only 2-fold in any of the strains tested; a finding similar to that reported by Redmond and Cohen (14).

Since phenobarbital is metabolized in vivo (15) it seemed possible that the pathway of metabolism of phenobarbital might be different in the substrains of rats. Therefore, an inhibitor of the microsomal drug-metabolizing system 2-diethylaminoethyl-2,2-diphenylvalerate-HCl (SKF 525A) was given to reactor animals receiving phenobarbital in an attempt to increase the liver supernatant aldehyde dehydrogenase activity. The "randomly bred" strains of rats (Sprague-Dawley, Long-Evans, Wistar and Charles-River) include animals of all three groups, RR, Rr, and RR. Inbred strains of rats (Fischer, Buffalo-Lewis, ACIF/MaI and BN/F MaI) are homozygous as expected.

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Effect of phenobarbital plus SKF 525-A on rat liver aldehyde dehydrogenase

Long-Evans rats (RR) were given either (a) phenobarbital 100 mg × kg⁻¹ the first day and 50 mg × kg⁻¹ on the two subsequent days, (b) SKF 525A, 25 µg × kg⁻¹ per day for 3 days in two divided doses, (c) both phenobarbital and SKF 525A, or (d) nothing. Liver supernatant aldehyde dehydrogenase was determined 16 hours after the last dose of phenobarbital.

| Dose            | Control   | Phenobarbital treated |
|-----------------|-----------|-----------------------|
|                 | nmoles NADH × protein⁻¹ × 5 min⁻¹ |                       |
| None            | 54.0 ± 4.8 (13) | 228.9 ± 21.6          |
| SKF 525A 25 mg × kg⁻¹ | 19.1 ± 1.4 (4)  | 257.3 ± 23.8          |
| SKF 525A 50 mg × kg⁻¹ | 43.5 ± 0.3 (3)  | 201.5 ± 20.4          |

* ± S. E. M. (number of animals).

Effect of phenobarbital treatment on liver aldehyde dehydrogenase and other liver enzymes

Sprague-Dawley rats (randomly selected) were given 100 mg × kg⁻¹ × day⁻¹ × 3 days of phenobarbital. The livers were removed and the various assays carried out as described in the text. The results are tabulated for the phenobarbital groups on the basis of the aldehyde dehydrogenase assays.

| Enzyme                          | Control | Phenobarbital (nonreacting) | Phenobarbital (reacting) |
|---------------------------------|---------|-----------------------------|--------------------------|
|                                 | Specific activity ± S. E. M. (u) | Specific activity ± S. E. M. (u) |                        |
| Alddehyde dehydrogenase         | 19.7 ± 1.2 (8) | 29.1 ± 1.6 (4) p < 0.05 | 83.9 ± 12.8 (4) p < 0.001 |
| Aniline hydroxylase             | 23.1 ± 1.9 (8) | 53.4 ± 5.4 (4) p < 0.001 | 65.1 ± 4.3 (4) p < 0.001 |
| Alcohol dehydrogenase           | 123.9 ± 17.8 (8) | 94.9 ± 9.9 (13) p < 0.2 | 84.5 ± 12.9 (7) p < 0.2 |
| Lactic dehydrogenase            | 2878.0 ± 28.0 (9) | 224.0 ± 95.0 (7) p < 0.1 | 2319.0 ± 65.0 (13) p < 0.1 |
| α-Glycerophosphate dehydrogenase| 14.3 ± 1.98 (7) | 26.1 ± 3.8 (6) p < 0.05 | 22.6 ± 2.4 (8) p < 0.05 |

* Specific activity for aldehyde dehydrogenase is measured as nanomoles of NADH formed × mg of protein⁻¹ × 5 min⁻¹, for aniline hydroxylase as nanomoles of p-aminophenol formed × mg of protein⁻¹ × hour⁻¹; for alcohol and lactic dehydrogenase as nanomoles of NADH formed × mg of protein⁻¹ × min⁻¹, and for α-glycerophosphate dehydrogenase as nanomoles of NADH formed.

Discussion

The present and previous studies (2) provide evidence that treatment of rats with phenobarbital induces a genetically determined, 10-fold increase in the activity of the NAD-dependent aldehyde dehydrogenase in liver supernatant. This is probably not a maximal effect, since even at a dose of 100 mg × kg⁻¹ × day⁻¹ for 3 days, the dose response curve is still rising (17). The effect is confined to one aldehyde dehydrogenase in the liver to the exclusion of both a second supernatant NAD-dependent aldehyde dehydrogenase and a mitochondrial aldehyde dehydrogenase. The half-time for decline in the stimulated activity is about 2.2 days (17) when plotted by the method of Swick et al. (18).

The effect is apparently unique to the liver. It is distinguished from other phenobarbital-induced increases in various enzymes on the basis of the following observations: (a) of the animals tested, the effect is confined to a genetically selected population animals that were either given phenobarbital or else were untreated. Administration of SKF 525A had no effect on the increase in aldehyde dehydrogenase activity produced by phenobarbital administration (Table V).

Table VI shows that aniline hydroxylase, a microsomal enzyme known to be induced by phenobarbital (11), is increased in both reacting and nonreacting animals. More recent studies in this laboratory of aminopyrine demethylation in the substrains (RR or RR) of Long-Evans rats also show that all animals respond to phenobarbital injection with a significant (p < 0.001) increase in the microsomal enzyme. Several other supernatant, NAD-dependent enzymes were also examined for any change in activity following phenobarbital administration; no marked differences were found (Table VI).

The increased aldehyde dehydrogenase activity after phenobarbital treatment apparently is confined to the liver; neither the kidney nor brain supernatant enzymes are affected (Table VII).

Although adrenalectomy is known to alter other enzyme systems (16), this procedure had no effect on the increase in aldehyde dehydrogenase elicited by phenobarbital. Administration of hydrocortisone 50 mg × kg⁻¹ × day⁻¹ for 3 days to normal reacting and nonreacting animals (RR) animals also did not bring about an increase in enzyme activity.

Table VII

Effect of phenobarbital administration on supernatant aldehyde dehydrogenase of various tissue of rats

Rats (Long-Evans Rr) were treated with phenobarbital (100 mg × kg⁻¹ × day⁻¹ × 3 days). Supernatant aldehyde dehydrogenase was assayed as described in the text with propionaldehyde as substrate.

| Tissue            | Control | Phenobarbital |
|-------------------|---------|---------------|
|                   | nanomoles NADH × mg protein⁻¹ × 5 min⁻¹ |                   |
| Liver             | 54.0 ± 4.8 (13) | 263.4 ± 7.4 (4) |
| Kidney            | 7.2 ± 0.0 (1)  | 11.4 ± 2.6 (4) |
| Brain             | 3.7 ± 0.1 (10) | 4.3 ± 0.2 (11) |

* ± S. E. M. (number of animals).
Since the kinetic characteristics of the enzymes from treated reactor (RR) and nonreactor (rr) animals are similar, we tentatively conclude that the enzymes are the same. Further purification and characterization of the enzymes from the livers of reactor and nonreactor animals is underway.

It is of interest that the apparent $K_m$ values for aldehydes obtained with this aldehyde dehydrogenase from rat liver are 2 to 3 orders of magnitude higher than are those of the corresponding enzymes from beef (7), human (19, 20), or horse liver (21) or from beef brain (22). Although this property makes kinetic studies somewhat easier, the physiological significance of the rat liver enzyme which exhibits these higher $K_m$ values is as yet unknown.

There seems to be little doubt that there are two soluble NAD-dependent aldehyde dehydrogenase enzymes present in rat liver. The first line of evidence supporting this conclusion is the marked increase in activity of aldehyde dehydrogenase toward some substrates but not others when phenobarbital is administered to susceptible animals. The second line of evidence is the additive character of the rates of NAD reduction observed when propionaldehyde and $p$-carboxybenzaldehyde are present in quantities which saturate each enzyme. The calculated and observed rate of NADH production in the presence of both substrates is nearly the same if one assumes the presence of two enzymes. This observation also affords presumptive evidence that $p$-carboxybenzaldehyde is not an effective inhibitor of the propionaldehyde enzyme nor is propionaldehyde an effective inhibitor of the $p$-carboxybenzaldehyde enzyme. The differential sensitivity of these enzymes to disulfiram also illustrates that two enzyme activities are present. Finally, the markedly different heat denaturation curves for aldehyde dehydrogenase when propionaldehyde and $p$-carboxybenzaldehyde are used as substrates provides strong evidence for the presence of two enzymes. The enzyme which oxidizes $p$-carboxybenzaldehyde may not be the one responsible for the oxidation of glyceraldehyde and glyceraldehyde. Glyoxaldehyde is a substrate for lactic dehydrogenase and this enzyme may account for the activity observed (23). The amount of each of these substrates oxidized by the inducible enzyme or other enzymes will have to await further purification of these enzymes. Recently, Shum and Blair (24) have presented evidence of two aldehyde dehydrogenases in rat liver supernatant.

The normal physiological role of the enzyme aldehyde dehydrogenase is presumably the oxidation of endogenous aldehydes such as those arising from deamination of various amines, e.g., norepinephrine, dopamine, serotonin, tryptamine, and histamine. This enzyme also functions in the oxidation of large quantities of exogenous aldehydes, such as those arising from deamination of various amines, e.g., norepinephrine, dopamine, serotonin, tryptamine, and histamine. This enzyme also functions in the oxidation of large quantities of exogenous aldehydes, such as acetaldehyde. There is no evidence at present to indicate that this hepatic enzyme becomes rate-limiting in any physiologically normal situation, so that an increase in activity of the enzyme may not be reflected in a physiologically demonstrable way. Experiments are underway to determine whether or not the rate of acetaldehyde oxidation is altered in vivo by phenobarbital treatment of reactor or nonreactor rats.

In this regard, Horton (25) has reported a slight stimulation of rat liver mitochondrial aldehyde dehydrogenase by chronic ethanol feeding. It is unlikely that the small increase in activity can be considered important unless it can be shown that the enzyme is rate-limiting in the normal condition. To date this has not been demonstrated. It is true, of course, that if one inhibits the enzyme, e.g., with disulfiram, this enzyme does become rate-limiting for oxidation of aldehydes (26).

The findings reported in this paper demonstrate some of the properties of an NAD-dependent aldehyde dehydrogenase in the supernatant fraction of livers from genetically selected rats. This enzyme can be markedly increased by phenobarbital administration. The availability of these genetically selected strains of rats affords an unique opportunity to investigate the mechanism of this phenomena. Whether or not this represents a net increase in enzyme protein must await further experiments.

Attempts to inhibit the reaction with protein synthesis inhibitors has not been satisfactory because of the mortality rate after several days treatment with these compounds and also because of their interaction with phenobarbital.

The demonstration of a second enzyme in the supernatant fraction of rat liver which is resistant to induction by phenobarbital and which catalyzes the oxidation of $p$-carboxybenzaldehyde, and perhaps other aldehydes as well is of considerable interest since this is an indication that not all aldehydes are oxidized by a single nonspecific NAD-dependent enzyme.

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