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EFFECT OF TRIIODOTHYRONINE ON ALCOHOL DEHYDROGENASE AND ALDEHYDE DEHYDROGENASE ACTIVITIES IN RAT LIVER

IMPLICATIONS FOR THE CONTROL OF ETHANOL METABOLISM

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Abstract—Treatment of rats with 20 μg of 3,3′,5-triiodo-L-thyronine (T3) per 100 g body wt for a period of 6 days led to a 45% decrease in total liver alcohol dehydrogenase and a 36% decrease in total liver aldehyde dehydrogenase. Most of the latter decrease was directly attributable to a 57% fall in the level of the physiologically-important low K_m mitochondrial isoenzyme. The high K_m isoenzyme of the post-mitochondrial and soluble fractions was much less affected by T3-treatment. T3, at concentrations up to 0.1 mM, did not inhibit the activity of aldehyde dehydrogenase *in vitro*. Despite these large losses of the two enzymes most intimately involved in ethanol metabolism, the rate of ethanol elimination *in vivo* was the same in T3-treated and control animals. Moreover, there was no difference between the two groups in the susceptibility of ethanol elimination to inhibition by 4-methylpyrazole, making it unlikely that an alternative route of ethanol metabolism had been significantly induced by treatment with T3. As it had been suggested that T3 might create a "hypermetabolic state" in which constraints normally imposed on alcohol dehydrogenase and aldehyde dehydrogenase are removed, thereby compensating for any loss in total enzymic activity, 2,4-dinitrophenol (0.1 mmoles/kg body wt) was administered to rats in order to raise the general metabolic rate. However, the uncoupler proved to be lethal to T3-treated animals and did not stimulate ethanol elimination in controls. The results do not support the notion that ethanol elimination *in vivo* is normally governed either by the level of alcohol dehydrogenase or by that of hepatic aldehyde dehydrogenase. However, the mode of control remains unclear.

During the last few years several studies have pointed to the level of hepatic alcohol dehydrogenase as the major determinant of the rate of ethanol metabolism in the rat [1–6]. However, the effects of certain hormones on the rate of ethanol elimination and on the activity of liver alcohol dehydrogenase provide only equivocal support for this idea. Although gonadectomy or administration of testosterone or oestradiol lead to parallel and quantitatively similar changes in alcohol dehydrogenase activity and the *in vivo* ethanol elimination rate [7–9], thyroidectomy or administration of thyroid hormones lead to changes in alcohol dehydrogenase activity without accompanying changes in the elimination rate [10–13]. It has been suggested that thyroid hormones, while depressing alcohol dehydrogenase activity, stimulate the microsomal ethanol oxidizing system (MEOS) thereby compensating for any lowering of the ethanol elimination rate due to the decrease in alcohol dehydrogenase [14, 15]. This idea remains to be tested *in vivo*. Another view is that thyroid hormones induce a hypermetabolic state which promotes the activity of the remaining alcohol dehydrogenase through the more rapid reoxidation of cytosolic NADH [11].

An alternative proposal for the control of ethanol metabolism [16–18] is that while flux through the main ethanol metabolizing pathway might ultimately be regulated at the level of alcohol dehydrogenase, one of the most important control factors could be the intrahepatic concentration of acetaldehyde which is determined by the activity of aldehyde dehydrogenase as well as alcohol dehydrogenase [19, 20]. It is, therefore, conceivable that flux through the pathway is more sensitive to the level of aldehyde dehydrogenase than to the level of alcohol dehydrogenase.

In the work presented here an attempt has been made to clarify the relationship between the ethanol elimination rate and the activities of both alcohol dehydrogenase and aldehyde dehydrogenase in the liver. Because of the previous reports concerning the apparently paradoxical effects of thyroid hormones, and the explanations put forward for those effects, the current work was directed towards elucidating the influence of 3,3′,5-triiodo-L-thyronine on the various parameters.

MATERIALS AND METHODS

Chemicals. 3,3′,5-Triiodo-L-thyronine (sodium salt), 4-methyl pyrazole hydrochloride and rotenone were purchased from Sigma Chemical Co. (St Louis, MO). NAD and yeast alcohol dehydrogenase were obtained from Boehringer Mannheim Australia Pty. Ltd., North Ryde, Australia and ethanol was from Ajax Chemicals, Sydney, Australia. L-Lysine monohydrochloride, sodium deoxycholate and acet-

aldehyde were purchased from BDH Ltd., Poole, U.K. The acetaldehyde was redistilled before use. All other chemicals were AR grade.

Treatment of animals. Female Wistar rats weighing between 240 and 300 g were used for all experiments. Test animals received a single subcutaneous injection of triiodothyronine (20 μg/100 g body wt) daily for 6 days prior to further experimentation. The triiodothyronine (T3) was in the form of a 200 μg/ml solution in 0.9% (w/v) NaCl containing 4 mM NaOH. Control animals received injections of alkaline saline lacking T3. Food and water were provided *ad libitum* throughout the period of treatment.

Ethanol elimination studies. Test and control animals were given an intraperitoneal injection of ethanol (2.5 g/kg body wt) in the form of a 12.5% (w/v) solution in 0.9% (w/v) NaCl. In one experiment two ethanol elimination studies were performed with the same groups of rats on successive days. In the first, ethanol alone was administered whereas in the second, the ethanol solution also contained 20 mM 4-methylpyrazole so as to deliver this substance at a dose of 0.4 mmoles/kg body wt. Blood samples (10 μl) were taken from the tail vein 90 min after administration of ethanol and at 45-min intervals thereafter until 6 hr had elapsed from the time of dosing. Each blood sample was immediately mixed with 0.2 ml of 0.6 M perchloric acid in a capped micro-test tube and was then centrifuged rapidly to remove the protein precipitate. Samples of the supernatant fluid were taken for ethanol analysis. Blood ethanol concentrations were plotted against time and the elimination curve was extrapolated to zero ethanol to determine the time taken for complete elimination. Total body water was calculated by extrapolating the linear portion of the curve to zero time. It was assumed that ethanol was distributed evenly throughout the body water and that the water content of each blood sample was 80% by volume. Any elimination curves that gave unrealistically high values for total body water were deemed to be unreliable and were disregarded [2]. Elimination rates were calculated as moles/min per g liver, mmoles/hr per kg body wt, and mmoles/hr per litre of blood. The three expressions were used so as to avoid being misled by any variations in body wt, liver wt or body water volume that might be caused by T3 treatment. It should be noted that, because ethanol can lead to hypothermia and reduced blood flow to the tail, all ethanol-treated animals were kept warm by placing them close to a radiant heater which maintained the air temperature in the cages at 28–32°.

Preparation of tissue for enzyme assay. On the morning following the ethanol elimination study, and approximately 17 hr after a final injection of T3 had been given to the test rats, the animals were killed by stunning and bleeding. The liver was quickly removed from each rat, weighed and placed in ice-cold 0.25 M sucrose solution. For alcohol dehydrogenase assays a 2-g portion of liver was homogenized with 8 ml of 50 mM HEPES buffer, pH 8.4, containing 0.33 mM dithiothreitol [21]. The homogenate was centrifuged at 40,000 *g* for 45 min and the supernatant fluid was used for the enzyme assay. For aldehyde dehydrogenase assays a 5 g portion of liver was homogenized with 20 ml of 0.25 M sucrose solution containing 10 mM Tris buffer, pH 7.4, and 1 mM EDTA [22]. The crude homogenate was centrifuged at 1100 *g* for 3 min to remove dense material and the supernatant was retained for further fractionation. An aliquot of the supernatant was treated with sodium deoxycholate to a final concentration of 0.3% (w/v) and was centrifuged at 40,000 *g* for 45 min. This concentration of deoxycholate was found to be optimal for the release of aldehyde dehydrogenase activity from mitochondria and other particulate material. The clear supernatant was designated "homogenate fraction" and was used for aldehyde dehydrogenase assays. Another 10 ml aliquot from the first low speed spin was centrifuged at 10,000 *g* for 15 min. The supernatant from this spin was divided into two equal portions to one of which was added sodium deoxycholate to a final concentration of 0.3% w/v. Both were then centrifuged at 40,000 *g* for 45 min. The supernatant fluid from the deoxycholate-treated portion was designated "post mitochondrial fraction" while that from the other portion was designated "soluble fraction" and was then treated with deoxycholate (0.3% w/v). The pellet from the 10,000 *g* spin was resuspended in 10 ml of homogenising medium and was resedimented by centrifuging at 10,000 *g* for 10 min. The washed pellet was finally resuspended in 10 ml of homogenising medium containing 0.3% w/v sodium deoxycholate and was centrifuged at 40,000 *g* for 45 min. The supernatant from this spin was designated "mitochondrial fraction". All preparative procedures were carried out at 0–4°.

Enzyme assays. Alcohol dehydrogenase activity was measured at 37° according to the general procedure of Crow *et al.* [21] adapted for a centrifugal analyzer system. The final reaction mixture comprised 0.5 M Tris buffer, pH 7.2, 2.8 mM NAD and 30 mM ethanol plus an appropriate amount of liver extract. Aldehyde dehydrogenase activity in the various liver fractions was measured at 37° in systems containing 50 mM potassium phosphate buffer, pH 7.4, 1.2 mM $MgCl_2$, 0.5 mM NAD, 0.2 mM 4-methylpyrazole, 2 μM rotenone, and 0.05 mM, 0.25 mM or 5 mM acetaldehyde [22].

Analyses. Ethanol present in the acidified blood samples was determined by the general method of Cornell and Veech [23] adapted for the centrifugal analyser. Protein was measured by the Biuret method using bovine serum albumin as the reference standard.

Data analysis. Lines were fitted to the elimination curves and to standard curves using the least squares method. Significance of difference was estimated by the Student's *t*-test and all results are presented as mean values ± the standard error of the mean.

RESULTS

The data in Table 1 show that the body wt of rats treated with T3 fell by almost 7% during the 6-day treatment period whereas the fall in control rats was less than 2%. However, liver wt, both in absolute terms and relative to either the pre-treatment or post-treatment body weight, was significantly greater in the T3-treated animals. This indicates that T3

Table 1. Effect of triiodothyronine on body wt and liver wt

Treatment	Body wt (g) Pre-treatment	Post-treatment	Liver (g)	Liver as a % of body wt % of pre-treatment body wt	% of post-treatment body wt
Control	268 ± 3	264 ± 3	7.72 ± 0.10	2.89 ± 0.04	2.94 ± 0.05
Triiodothyronine	265 ± 3	247 ± 3*	8.27 ± 0.12†	3.12 ± 0.04*	3.35 ± 0.05*

Triiodothyronine (200 μg/kg initial body wt) was administered by subcutaneous injection in the form of a 200 μg/ml solution in 0.9% (w/v) NaCl containing 4 mM NaOH. A single injection was given daily for 6 days. Control animals received injections of the alkaline saline solution lacking triiodothyronine. The results are presented as mean ± S.E.M. for 24 rats in each group.

* Significantly different from control $P < 0.001$.

† Significantly different from control $P < 0.002$.

caused a small increase in liver size over the treatment period despite the overall loss in body wt.

The effects of T3 on the activities of liver alcohol dehydrogenase and aldehyde dehydrogenase are presented in Table 2. The results are in accord with ones reported previously in that T3 caused a 50% decrease in alcohol dehydrogenase activity expressed on a "per g liver" basis representing a 45% fall in total liver alcohol dehydrogenase activity. However, somewhat unexpectedly, there was an even more pronounced decrease in the liver aldehyde dehydrogenase activity of T3-treated rats. In the "homogenate" fraction, shown in Table 2, the decrease was greatest when enzyme activity was assayed using 0.05 mM or 0.25 mM acetaldehyde suggesting that the low K_m isoenzyme was the one principally affected. This was confirmed by results obtained using other fractions of the liver homogenate (Table 3). Low K_m aldehyde dehydrogenase activity, over three quarters of which resided in the "mitochondrial" fraction, fell by 60–70% in the T3-treated rats whereas the high K_m activity, which was taken as the difference between activity measured with 0.05 mM acetaldehyde and that measured with 5 mM acetaldehyde, and most of which resided in the "post-mitochondrial" fraction, fell by only 10–30%. Aldehyde dehydrogenase activity in the "soluble" fraction was very low and was unaffected by T3-treatment.

Table 2. Effect of triiodothyronine on hepatic alcohol dehydrogenase and aldehyde dehydrogenase activities

Treatment	Alcohol dehydrogenase (μmoles/min per g liver)	Aldehyde dehydrogenase (μmoles/min per g liver) Acetaldehyde (mM) 0.05	0.25	5.0
Control	3.52 ± 0.18	1.45 ± 0.09	1.44 ± 0.09	3.29 ± 0.19
Triiodothyronine	1.75 ± 0.16*	0.58 ± 0.03*	0.59 ± 0.07*	2.25 ± 0.08*

Liver extracts were prepared as described in Materials and Methods, the homogenate fraction being used for aldehyde dehydrogenase. Activities were determined from initial rate measurements at 37° and are expressed as mean values ± S.E.M. for eight animals in each group.

* Significantly different from control. $P < 0.001$.

Table 3. Effect of triiodothyronine treatment on aldehyde dehydrogenase activity of different subcellular fractions of liver

Treatment	Acetaldehyde (mM)	Aldehyde dehydrogenase (μmoles/min per g liver) Mitochondrial fraction	Post-mitochondrial fraction	Soluble fraction
Control	0.05	1.13 ± 0.08	0.24 ± 0.02	0.19 ± 0.04
Triiodothyronine	0.05	0.37 ± 0.01*	0.15 ± 0.01*	0.18 ± 0.02
Control	0.25	1.05 ± 0.07	0.35 ± 0.03	0.32 ± 0.05
Triiodothyronine	0.25	0.40 ± 0.01*	0.18 ± 0.02*	0.30 ± 0.02
Control	5.0	1.47 ± 0.09	2.01 ± 0.17	0.65 ± 0.05
Triiodothyronine	5.0	0.86 ± 0.01*	1.39 ± 0.08*	0.64 ± 0.04

Fractions were prepared as described in Materials and Methods. The "post-mitochondrial" fraction includes enzyme activity derived from both the post-mitochondrial pellet and the "soluble" fraction. Activities were determined from initial rate measurements at 37° and are expressed as mean values ± S.E.M. for eight animals in each group.

* Significantly different from control. $P < 0.001$.

Table 4. Ethanol elimination rates in control and triiodothyronine-treated rats

Treatment	Body water (l/kg)	μmoles/min per g liver	Elimination rate mmoles/hr per kg body wt	mmoles/hr per l blood
Control (19)	0.63 ± 0.02	4.16 ± 0.13	7.36 ± 0.23	9.47 ± 0.36
Triiodothyronine (16)	0.71 ± 0.04	3.96 ± 0.15	8.01 ± 0.23	9.05 ± 0.47
Control (4) +4-methylpyrazole	0.64 ± 0.06	1.37 ± 0.22	2.34 ± 0.36	3.21 ± 0.59
Triiodothyronine (4) +4-methylpyrazole	0.62 ± 0.02	1.23 ± 0.03	2.53 ± 0.11	3.30 ± 0.23

Ethanol was administered intraperitoneally at a dose of 2.5 g (54.3 mmoles) per kg body weight and 4-methyl pyrazole at 0.4 mmoles per kg body wt. The number of animals in each group is shown in parentheses in the column on the far left. Rates are given as mean ± S.E.M.

Nonetheless, the loss of about 60% of total aldehyde dehydrogenase activity when acetaldehyde was present at 0.25 mM, a value that is probably close to the upper limit of hepatic acetaldehyde concentrations *in vivo*, represents a very substantial lowering of the acetaldehyde-oxidizing capacity of the liver. It should be noted that T3, when present at concentrations up to 0.1 mM in the aldehyde dehydrogenase assay system, had little or no effect on enzyme activity. Hence, the observed decrease in aldehyde dehydrogenase activity in T3-treated rats appears to be due to a fall in the enzyme level and not due to inhibition of the enzyme by the hormone.

While it might be expected that decreases of such magnitude in the activities of the two enzymes most intimately involved in ethanol metabolism would lead to a lowering of the rate of ethanol elimination *in vivo*, the data presented in Table 4 demonstrate that no such change occurred. The elimination rate, expressed in three different ways so as to obviate any problems arising from differences in liver wt, body wt or body water content, was invariably the same in T3-treated and untreated animals. Moreover, when 4-methylpyrazole, a potent inhibitor of alcohol dehydrogenase, was administered simultaneously with ethanol, the ethanol elimination rate was decreased to the same degree (approx. 70%) in both groups of animals. This suggests strongly that, even after treatment with T3, the alcohol dehydrogenase pathway remained dominant in ethanol oxidation and that no other pathway had been induced to any significant degree. More importantly, the results also suggest that, in the absence of methylpyrazole, the rate of flux through the alcohol dehydrogenase/aldehyde dehydrogenase pathway was not governed by the absolute level of either alcohol dehydrogenase or aldehyde dehydrogenase in the liver.

In an attempt to determine whether or not the maintenance of the ethanol elimination rate in T3-treated rats might be due to the existence of a hypermetabolic state involving the more rapid mitochondrial oxidation of NADH, a group of four control rats and three T3-treated rats were subjected to a second ethanol elimination study in which the uncoupler 2,4-dinitrophenol (0.1 mmoles/kg body wt) was co-administered with the ethanol. The intention of this experiment was to decide whether ethanol elimination in control rats might be more amenable to stimulation by an uncoupler than that in T3-treated animals. However, all T3-treated animals and one control died within 50 min following administration of ethanol and dinitrophenol. In all three control animals that survived, ethanol elimination in the presence of dinitrophenol was slower than in its absence (i.e. 87 ± 4%; range 82–94%). It appeared unlikely, therefore, that the use of uncouplers would yield valuable insights into the way in which the ethanol elimination rate is controlled.

DISCUSSION

In an erudite discussion on the control of metabolic flux Kacser and Burns [24] pointed out that to describe the process in confined terms such as "rate-limiting steps", "key enzymes" and "bottlenecks", is to oversimplify and dequantify what is, in reality, a complex and integrated, yet quantifiable phenomenon. However, they conceded that even though the control of flux through a metabolic pathway is most commonly shared among the various enzymes of that pathway with none having a dominant influence, there will be instances in which the rate of flux is especially sensitive to changes in the concentration or activity of one particular enzyme. It is in this sense that several groups of workers have suggested that alcohol dehydrogenase is rate-limiting for ethanol metabolism, and hence for ethanol elimination, in the rat. The various lines of evidence for this are (a) the maximum activity of hepatic alcohol dehydrogenase *in vitro* is close to the rate of ethanol elimination *in vivo* [1–4, 21]; (b) two inhibitors of alcohol dehydrogenase, 4-methylpyrazole and isobutyramide, exert qualitatively and quantitatively similar effects on alcohol dehydrogenase activity *in vitro* and ethanol elimination *in vivo* [6]; (c) diurnal variations in the level of alcohol dehydrogenase [5], or variations caused experimentally by sex hormones [7–9] or certain dietary regimes [25, 26] are accompanied by quantitatively similar changes in the rate of ethanol elimination; (d) strains of rats which have different hepatic alcohol dehydrogenase levels exhibit proportionately similar differences in their capacities to eliminate ethanol [27].

Despite the impressiveness of this evidence, however, the idea of alcohol dehydrogenase as the rate-limiting enzyme fails to explain, or even address some other relevant observations. One such obser-

vation is that certain conditions, including experimental uraemia [28], cold acclimation [29] and hypothyroidism [10, 12, 13], lead to changes in either the alcohol dehydrogenase level or the ethanol elimination rate without any concomitant change in the other. Another relevant observation is that the maximum *in vitro* activity of liver aldehyde dehydrogenase, when measured at acetaldehyde concentrations comparable to those thought to obtain *in vivo* (i.e. 0.01–0.25 mM [2, 20, 30]), is lower than that of alcohol dehydrogenase and, in general, lower than the ethanol elimination rate. Even allowing for the fact that not all ethanol is eliminated metabolically and that not all acetaldehyde need be metabolized in the liver, it still appears that liver aldehyde dehydrogenase is unlikely to be present at levels far in excess of what is required for the metabolic task it normally performs. Furthermore, as the low K_m isoenzyme, which constitutes roughly half of the total activity [31, 32 and this paper], and is accepted to be of greatest importance in ethanol metabolism [33, 34], is effectively saturated when the acetaldehyde concentration exceeds 0.01 mM, the responsiveness, or "elasticity" [24], of aldehyde dehydrogenase with respect to changes in the intrahepatic acetaldehyde concentration must be very low during ethanol metabolism. In an earlier paper [18] these considerations formed the basis of a speculative proposal for aldehyde dehydrogenase acting as a rate-limiting enzyme in ethanol metabolism, or at least taking a very prominent role in the control of flux through the ethanol metabolising pathway.

The current study was undertaken in order to seek an answer to the question of whether the level of alcohol dehydrogenase, or that of aldehyde dehydrogenase, might serve as the single most important governor of the *in vivo* ethanol elimination rate. Triiodothyronine-treatment was chosen as an experimental condition because it had previously been shown to depress strongly the level of liver alcohol dehydrogenase [10, 12], though its effect, if any, on aldehyde dehydrogenase had not been recorded. The results, however, suggest that it is not the amount of either enzyme in the liver that limits the rate of ethanol elimination *in vivo*. Despite falls of 45 and 57% respectively in total liver alcohol dehydrogenase and low K_m aldehyde dehydrogenase following treatment with T3, the elimination rate was unaltered.

The only way in which these observations can be reconciled with the idea of alcohol dehydrogenase normally acting as a rate-limiting enzyme is to infer that treatment with T3 caused much of the overall oxidation of ethanol to be accomplished by other mechanisms such as MEOS. This is the explanation put forward by Moreno and co-workers [14, 15] but is not supported by the present study in which it was found that ethanol elimination in T3-treated rats and control rats was equally susceptible to inhibition by 4-methylpyrazole. Though pyrazole and methylpyrazole have also been shown to scavenge hydroxyl radicals [35] and to interfere with ethanol oxidation by MEOS *in vitro* [35] and, possibly, *in vivo* [36], the dose of 0.4 mmoles methylpyrazole/kg body wt used in this work, chosen because it is well below toxic levels [37] and yet effectively inhibits ethanol metabolism via alcohol dehydrogenase even at high ethanol concentrations [6, 37, 38], is thought to be too low to have affected MEOS significantly, especially as the concentration of ethanol in animals treated with methylpyrazole remained high throughout the course of the 6-hr elimination experiment.

With respect to the possibility of hepatic aldehyde dehydrogenase normally playing a rate-limiting role in ethanol metabolism it should be noted that whatever mechanisms are involved in the oxidation of ethanol to acetaldehyde, the acetaldehyde has to be adequately dealt with because of its relatively high toxicity [39]. It is possible that as aldehyde dehydrogenase, unlike alcohol dehydrogenase, is fairly ubiquitous throughout the tissues, a fall in hepatic activity might lead to more acetaldehyde being oxidized extrahepatically. Alternatively, the high K_m isoenzyme might assume a more important role than usual if the acetaldehyde concentration in the liver rises sufficiently. However, in this study, no measurements were made of either blood or liver acetaldehyde levels so these possibilities remain purely speculative.

Perhaps the most acceptable explanation of the events observed in these experiments is that neither the alcohol dehydrogenase level nor the aldehyde dehydrogenase level *per se* is rate-limiting for ethanol elimination *in vivo* but that regulation of metabolic flux is brought about by the degree to which one or both enzymes are controlled by parameters such as substrate or inhibitor concentrations. Although analyses by Cornell [3] and Crabb *et al.* [4] suggested that alcohol dehydrogenase normally operates at about 70% of its maximum velocity, this appears incompatible with the fact that ethanol elimination can remain unaffected even in the face of a loss of about half the total liver alcohol dehydrogenase, especially when there is no evidence for an alternative eliminatory route being induced. If, however, alcohol dehydrogenase were normally to operate at less than half maximum velocity, a 50% fall in the enzyme level could be accommodated provided that the restrictions normally placed upon its activity were lifted so that it operated much closer to its maximum velocity. The same argument applies to aldehyde dehydrogenase. This is the essence of the ideas put forward by Israel and co-workers who, in a series of papers [11, 29, 40], maintained that the mitochondrial oxidation of NADH normally limits the rate of oxidation of ethanol and acetaldehyde, and that agents or conditions, such as uncouplers or increases in the intracellular ADP:ATP ratio, which stimulate mitochondrial oxidative activity also promote the ethanol metabolic rate. In the present study, however, no evidence for this hypothesis could be adduced and, unlike Israel *et al.* [41], we found no stimulation of ethanol elimination by 2,4-dinitrophenol. It was, nonetheless, interesting to note that the dose of dinitrophenol, though lower than that administered to rats by Israel *et al.* [41], seemed to be especially lethal to T3-treated animals, perhaps indicating that they were already in a hypermetabolic state.

The research being undertaken in this laboratory is aimed ultimately at finding ways of accelerating ethanol elimination that might be applied clinically

in cases of acute ethanol intoxication. It was at one time claimed that intravenous administration of T3 caused a 2-fold increase in the rate at which human patients eliminated ethanol [42] but this claim could not be substantiated in later work either with human subjects [43] or dogs [44]. The results of the present study also suggest that T3 has no role in this regard but keep open the possibility that ethanol elimination might be amenable to short-term stimulation even in the absence of increases in the levels of alcohol dehydrogenase and aldehyde dehydrogenase in the liver.

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