tion (Table 1). At comparable doses, the reduction was approximately equal to that obtained with a preparation of human EGF (hEGF) (*12*) isolated from human urine. In contrast, the biological activity of PDGF (*8*) remained constant under the same experimental conditions (Table 1). The finding that antibodies to EGF specifically removed the mitogenic activity from SM-B preparations is compatible with the view that the biological activity resided in EGF or material immunologically cross-reacting with EGF. Considering the high molar ratio of SM-B to EGF antibody (12:1) used in this experiment, it is unlikely that the decrease in mitogenic activity was due to precipitation of the SM-B molecule itself. The presence of EGF-like material in the preparation of SM-B was further indicated by its reactivity with the EGF receptor. The preparation of SM-B competed with ^{125}I-labeled EGF for binding to cultured glial cells, 10 μg of SM-B containing the equivalent of about 2 ng of EGF (not shown). If one assumes that this material has the same mitogenic properties as authentic EGF its presence is thus sufficient to explain the entire stimulatory activity of SM-B. The degree of contamination (about 0.02 percent EGF in the SM-B preparation) is, however, so small that it would escape detection by conventional chemical methods.

An enhancing effect of SM-B on protein synthesis (incorporation of leucine) in vivo has been reported (*13*). In view of the present findings it is possible that this activity should not be ascribed to SM-B itself; the effects of EGF in vivo are well documented in other systems (*14*).

In conclusion, the biological activity by which SM-B was originally defined, that is, stimulation of DNA synthesis in human cultured glial cells (*2*), seems to reside in EGF, a minor contaminant of the preparation; the major component of SM-B is not a growth factor in this system. Therefore, although circulating levels of SM-B, as determined by radioimmunoassay, may vary with the growth hormone status of the individual (*15*) there is not sufficient evidence to justify the term somatomedin for this substance.

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16. We thank L. Rask for antiserum to mEGF and for hEGF and A. Magnusson, M. Kastemar, F. Carlsson, and Y. Öhgren for excellent technical assistance. This work was supported by grants from the Swedish Cancer Society (55 and 689), the Swedish Medical Research Council (4486 and 03X-4), Svenska Sällskapet för Medicinsk Forskning, and Uppsala University.

3 March 1981; revised 29 April 1981

Ethanol Reveals Novel Mercury Detoxification Step in Tissues

Abstract. *Volatile mercury was produced de novo by mouse tissue homogenates that contained mercuric ions. Ethanol stimulated the release of tissue mercury into the vapor phase, and the mechanism appears to be an inhibition of reoxidation of volatile mercury. Components responsible for mercury volatilization are heat-labile. The highest volatilizing activity in the liver is associated with the soluble fraction obtained after centrifugation at 105,000g.*

Biotransformation of mercurials, leading to volatilization of the elemental vapor (Hg^0), occurs in microorganisms. In mercury fungicide- or drug-resistant prokaryotes, volatilization of this metal is a detoxifying mechanism (*1*). In contrast to microbial systems, mammalian mechanisms for transforming mercury into volatile products have been largely unexplored. This pathway in higher animals was first proposed by Clarkson and Rothstein (*2*) upon detection of volatilized mercury from rats injected with $HgCl_2$; additional evidence came from a study showing mercury exhalation in human volunteers who had been exposed to mercury vapor (*3*). Studies of laboratory animals have demonstrated the existence of a metabolic route for de novo Hg^0 generation and the ability of ethanol to enhance exhalation of the metal (*4, 5*). None of these studies have characterized the tissue site or sites or the biochemical nature of the interaction between ethanol and the Hg^0-generating pathway. We describe the ethanol-stimulated conversion of Hg^{2+} to volatile mercury by mouse tissues in vitro, the subcellular fractions involved, and a plausible mechanism for the ethanol effect.

Mercury volatilizing activity (MVA) in CBA/J mouse liver and kidney homogenates or fractions was estimated by the release of radioactive mercury from the tissue suspensions into the vapor phase during 30-minute incubations (*6*). The ^{203}Hg-labeled (New England Nuclear) $HgCl_2$ had been equilibrated with excess L-cysteine (Sigma) to ensure that all mercury added to tissues was in the Hg^{2+} form and attached to thiol groups, namely, mercury-cysteine complex. The final mercury concentration before MVA assays was 0.16 μ*M* in all tissue preparations.

Liver and kidney homogenates incubated in the presence of the mercury-cysteine complex and alcohol showed ethanol-dependent increases in the amount of radioactivity released into the vapor phase (Fig. 1). Increasing initial ethanol concentrations above 100 mg/dl elicited no further enhancement of MVA in kidney homogenates. With liver samples, incremental increases in MVA were obtained with ethanol concentrations of up to about 400 mg/dl. Maximal volatilizations in 30 minutes averaged 0.12 and 0.19 percent of the added mercury for kidney and liver homogenates, respectively.

We determined that treating liver homogenates with heat (74°C water bath for 10 to 15 minutes) eliminated MVA regardless of the presence of ethanol. Residual mercury volatilizations in these samples amounted to about 8 pg of Hg in 30 minutes or 0.008 percent of the mercury added to the suspensions. Heat inactivation is usually evidence of heat lability of the component or components necessary for the process. With mercury, however, heat denaturation may create additional binding sites (that is, by

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unfolding of proteins) and thus effectively sequester the metal from active sites or processes that are not heat-labile. To examine this possibility, equivolume additions of buffer containing 0, 2.5, 25, 50, 75, or 100 mg (wet weight) of fresh homogenized liver were made to flasks containing heat-deactivated tissue and maximal stimulatory concentrations of ethanol. Tests were otherwise conducted as above. We observed higher volatilizations with increasing wet weights of fresh tissue (*7*). The maximum rate of volatilization (approximately 52 pg of Hg per 30 minutes) was less than that obtained with an equivalent wet weight of tissue assayed without the heat-deactivated homogenate (Fig. 1), indicating that sequestration of some Hg^{2+} had occurred. Nevertheless, these results demonstrated that some Hg^{2+} was still available for the volatilization process when heat-treated homogenates were tested alone. We concluded that a heat-labile component was necessary for mercury volatilization.

To locate the active component responsible for MVA, fresh liver fractions were added to heat-deactivated suspensions and tested under conditions identical to those used for whole-homogenate additions (*8*). Table 1 shows that higher activities (per milligram of fresh protein) were associated with the soluble components and, when compared with results obtained from whole-homogenate additions, an apparent fourfold increase in MVA was obtained in the 105,000*g* supernatant.

We assumed that Hg^0 was the volatilized product because mice exhale Hg^0 after treatment with $HgCl_2$ (*4, 5*). Furthermore, the presence of excess cysteine and tissue protein ensured that ionic mercury was bound to thiol groups and was therefore nonvolatile. Hg^0 is predominantly, if not solely, oxidized by catalase through the peroxidatic mechanism (*9*), but this action can be blocked by methanol, ethanol, or 3-amino-1,2,4-triazole (AT) (*10*). A simple explanation for the ethanol effect in our study was that, by inhibiting Hg^0 oxidation, ethanol caused our tissue samples to be rich in Hg^0 and thereby favored the escape of Hg^0 into the vapor phase. If this explanation was correct, other catalase inhibitors should also increase mercury volatilization. We tested this by using AT alone or with ethanol in fresh liver homogenates. Our results (*11*) indicated that the presence of AT led to increases in mercury volatilization over control values, and volatilizations obtained with both ethanol and AT in the same sample were higher than those obtained with either agent alone (*12*).

To exclude the mercury-cysteine complex as the only substrate for MVA, experiments were repeated with homogenates obtained from mice that had been treated with $^{203}HgCl_2$. The results demonstrated the following: (i) MVA can be detected without supplementation with the mercury-cysteine complex, thus precluding MVA being linked to the presence of added cysteine; (ii) MVA in both liver and kidney homogenates was stimulated in the presence of ethanol; and (iii) volatilization was greater in kidney homogenates than in the liver homogenates (based on wet weights) because the metal accumulates in the kidneys (*13*).

We conclude that mammalian cells demonstrate a biochemical similarity to some microorganisms with respect to ionic mercury reduction. Inasmuch as Hg^{2+} reduction and subsequent volatilization of Hg^0 results in diminished mercury concentrations at the tissue sites, we recognize $Hg^{2+} \rightarrow Hg^0$ as a detoxification step similar to that in mercury-resistant microorganisms. Our results,

Table 1. Mercury volatilization rates are shown in whole liver homogenates and fractions in the presence of deactivated tissue. Liver fractions were prepared by centrifugation at 600*g* for 10 minutes; the 600*g* pellets were discarded and the supernatants centrifuged for 10 to 20 minutes at 8000*g*. The 8000*g* pellets were washed twice and resuspended in phosphate buffer at 5 to 10 percent (weight per volume). The supernatants of 10 percent homogenates were centrifuged at 105,000*g* for 1 to 2 hours, and the pellets were resuspended to a 5 to 10 percent concentration. Tests for marker enzymes were not attempted on ultracentrifuge fractions. Average protein concentrations in liver fraction suspensions were 5.3 and 8.3 mg/ml for the 8000*g* supernatants and pellets, respectively, and 9.6 and 13.5 mg/ml for the 105,000*g* supernatants and pellets, respectively. The method of Lowry *et al.* (*22*) was used for protein determinations.

Suspension	Volatilization of Hg	
	Normalized activity* (pg/mg protein per 30 minutes)	Relative activity† (%)
Whole homogenate	2.3 ± 0.5 (5)	100
*Centrifugation at 8000*g		
Pellet	0.4 ± 0.1 (5)	17
Supernatant	6.0 ± 1.8 (14)	261
*Centrifugation at 105,000*g		
Pellet	0.7 ± 0.2 (5)	30
Supernatant	10.6 ± 1.3 (6)	461

*Net rate of mercury volatilizations, obtained in the presence of maximal stimulatory ethanol concentrations, were normalized on the basis of the amount of fresh protein added. Data are reported as means ± S.D. Numbers in parentheses represent the number of determinations. †The mean net volatilization with 100 mg (wet weight) of fresh whole tissue added to the deactivated suspension was used as the reference rate (100 percent). This whole homogenate stock contained 94 mg of protein per 500 mg of liver (wet weight) per milliliter of suspension.

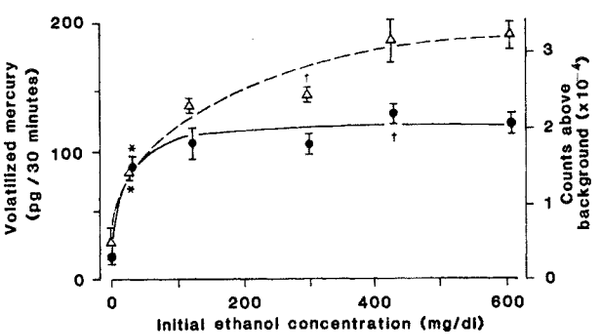

Fig. 1. Mercury volatilizing activity in liver (△) and kidney (●) homogenates supplemented with a mercury-cysteine complex. Weighed minced livers or kidneys from three or four mice were prepared in oxygen-saturated ice-cold phosphate buffer (0.1*M*, *p*H 7.4) and ground (Kinematica) for several seconds with enough buffer to yield 5 percent (wet weight per volume) suspensions. Each flask contained 2 ml of the homogenate plus the mercury-cysteine complex and saline-ethanol solutions. Final tissue concentration was 3.3 percent (weight per volume); assays were performed in a shaking water bath at 37°C. Ethanol (95 percent) was diluted with saline and equivolume additions to flasks generated the initial concentrations. Control flasks received saline only. The mercury-cysteine complex was prepared from ^{203}Hg-labeled $HgCl_2$ in 0.5*M* HCl, which was transferred by pipette into a 25-ml midget impringer (Bendix) with the exit opening connected by a vacuum line to a Hopcalite filter placed in a gamma-counter well. Laboratory air was passed through the impinger at 1 liter per minute while a freshly prepared 2 μ*M* cysteine solution (aqueous) was added to the isotope solution to yield a cysteine to mercury molar ratio of 200:1. Addition of 0.5*M* NaOH to neutralize the *p*H was followed by enough distilled, deionized water to yield 100 ng of Hg per milliliter of solution; N_2 was bubbled through the solution in the impinger for several minutes to eliminate any trace of volatile mercury. A flat response (no increase) on the gamma spectrometer recordings confirmed the success of the purging procedure. Then 1-ml portions were added to the flasks. Data are means ± S.E. (N = 5); asterisk indicates a statistically significant difference from controls ($P < .05$, Student's t-test); dagger indicates N = 4.

together with those on the catalase oxidation of Hg^0 to Hg^{2+}, indicate the presence of an oxidation-reduction cycle for mercury in mammalian cells, the oxidation step being in the peroxisomes and the reduction step in the cytoplasm. Since most organomercury compounds degrade to Hg^{2+} in mammalian tissue, Hg^0 should be present in tissues after exposure to virtually all forms of organic or inorganic mercury. Hg^0 may play an important general role in the physiological distribution of the metal after administration of all forms of mercury because of its lipid solubility and high diffusibility (*14*).

The elucidation of mercury oxidation and reduction pathways shows that our concepts which restrict the role of metallic cations to enzyme inhibition must be revised. Mercury acts not only as an enzyme inhibitor but as substrate for oxidation-reduction reactions, much like organic xenobiotics (*15*). Reactions in which a metal serves as substrate, such as oxidation-reduction [Hg, Cr (*16*), As (*17*), and Ni (*18*)] and alkylation-dealkylation [Hg (*19*), As (*20*), and Sn (*21*)] will probably be an important focus for future heavy metals research.

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6. Modified 15-ml Warburg flasks were used, and continuous air flow (100 ml per minute) above the tissue preparation swept volatilized mercury onto a Hopcalite (Mine Safety Appliances) adsorbent which was counted for radioactivity. Recoveries of known amounts of $^{203}Hg^0$ generated in these flasks were 98.8 ± 5.1 percent [mean ± standard deviation (S.D.)]
7. Actual results in picograms of Hg per 30 minutes [means ± standard error (S.E.), $N = 5$] were: 8.1 ± 2.0, 10.9 ± 1.4, 33.0 ± 1.7*, 46.4 ± 1.9, 52.2 ± 2.8, 49.3 ± 2.5 for 0, 2.5, 25, 50, 75, and 100 mg of fresh liver, respectively (*statistically significant difference from control values, $P < .05$, Student's *t*-test). All flasks contained standard amounts of heat-deactivated tissue, mercury-cysteine complex, and ethanol (613 mg/dl, initially). Control flasks received buffer only.
8. This protocol was used despite the depression of maximal mercury volatilization in the presence of deactivated tissue because the background (residual) volatilization was low, the experimental reproducibility high, and the method facilitated comparison of specific MVA.
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11. AT, an irreversible inhibitor of catalase activity [T. R. Tephly, G. J. Mannering, R. E. Parkes, *J. Pharmacol. Exp. Ther.* **134**, 77 (1961)], was dissolved in saline (250 mg of AT per milliliter). Fresh liver homogenates were incubated in 90 m*M* AT for 1 hour at 4°C before MVA tests. Control homogenates received only saline. The mercury-cysteine complex and either ethanol or saline were added after the incubation period. Ethanol (where added) was initially 123 mg/dl (27 m*M*). Final tissue concentration in all flasks was 3.3 percent (weight per volume). Amounts of Hg (in picograms) volatilized in 30 minutes (means ± S.E., $N = 5$) were: controls, 19.8 ± 3.9; AT, 98.2 ± 4.6*, ethanol, 109.3 ± 3.7*; AT ± ethanol, 155.6 ± 7.3** (*significantly different from control values, $P < .05$, Student's *t*-test; **significantly different from values obtained with either AT or ethanol alone, $P < .05$, Student's *t*-test).
12. Ethanol-derived acetaldehyde has been reported to decrease reduced glutathione in isolated hepatocytes [J. Vina *et al.*, *Biochem. J.* **188**, 549 (1980)]. Conceivably, decreased concentrations of glutathione could contribute to increased mercury volatilization in our ethanol experiments by decreasing thiol sites available for mercury binding. Although the exact relation of glutathione to MVA is not known, we believe its role, if any, is a minor one because cysteine, which readily forms adducts with acetaldehyde [A. I. Cederbaum and E. Rubin, *Biochem. Pharmacol.* **23**, 2179 (1976)] was added in excess to our incubation media and increased MVA was observed with AT alone.
13. Two mice were injected intraperitoneally with 0.5 mg of Hg per kilogram as $^{203}HgCl_2$ and 48 hours later checked for mercury exhalation (*4*). Animals were then killed and 5 percent (weight per volume) homogenates made from pooled mouse livers or kidneys. Mercury concentrations were determined from samples of each homogenate, and the remainder was tested for MVA, with or without ethanol. Initial mercury concentrations in the incubation media, as determined by radioactivity counting, were 24 ng for liver and 488 ng for kidneys [natural background total (organic plus inorganic) mercury concentrations in untreated CBA/J mice were < 1.5 ng/ml and ≤ 3.3 ng/ml for 5 percent liver and kidney homogenates, respectively]; initial ethanol concentrations were either 31 (low) or 613 mg/dl (high). Final tissue concentration in all flasks was 3.2 percent. Results of 30-minute tests in picograms of Hg (means of duplicate or triplicate results) were: control (no ethanol) liver, < 1; control (no ethanol) kidney, 20; low ethanol liver, ~ 3.5; low ethanol kidney, 140; high ethanol liver, 11.8; high ethanol kidney, 230.
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15 December 1980; revised 25 February 1981

Brown Adipose Tissue: Thermic Response Increased by a Single Low Protein, High Carbohydrate Meal

Abstract. *The weight of interscapular brown fat in the rat and its rate of respiration increased in response to a single meal. These data suggest that brown adipose tissue plays a role in the thermic effect of meals and that diet-induced thermogenesis may reflect the summation of the thermic effects of single meals during prolonged overeating.*

Brown adipose tissue in the rat increases its thermogenic activity in response to long-term overfeeding (*1*). Our data suggest that this same tissue may play a role in the thermic response to a single meal.

Increased oxygen uptake after a meal was first reported by Lavoisier in 1789 (*2*). Rubner (*3*) called this phenomenon the specific dynamic effect (SDE) and ascribed the elevation in heat production after a meal to energy wasted in the ensuing metabolic processes. The nature of the reactions leading to the production of SDE, however, is still not clear; and SDE has been regarded as an expression of energy lost in the process of digestion and absorption (*4*), amino acid oxidation and urea formation (*5*), protein synthesis (*6, 7*), and other metabolic conversions (*8*). The effect was found by some to be considerably greater after a protein meal than after a carbohydrate or a fat meal (*3, 9*), while others found it to be unrelated to the type of the macronutrient consumed (*7, 10, 11*). When mixed meals are offered, the total SDE is considerably smaller than the sum of SDE's produced when each macronutrient is provided separately (*10, 12, 13*). The organ primarily responsible for SDE has not been clearly identified, although the liver has been considered to play an important role (*14*).

0036-8075/81/0904-1125$01.00/0