Swift increase in alcohol metabolism (SIAM): understanding the phenomenon of hypermetabolism in liver

Blair U. Bradforda, Ivan Rusynb,*
a357 Rosenau Hall, Department of Environmental Sciences and Engineering, School of Public Health, University of North Carolina, Chapel Hill, NC 27599-7431, USA
bBowles Center for Alcohol Studies, School of Medicine, University of North Carolina, Chapel Hill, NC, 27599-7178, USA

Received 25 June 2004; received in revised form 16 November 2004; accepted 4 December 2004

Abstract

The swift increase in alcohol metabolism (SIAM) is a phenomenon defined as a rapid increase in hepatic respiration and alcohol metabolism after administration of a bolus dose of alcohol. Continuous exposure to alcohol is known to produce adaptive changes in liver alcohol and oxygen metabolism. A considerable burst of hepatic respiration can also occur after administration of a single large dose of alcohol and results in a near doubling of alcohol metabolism, a high demand for oxygen, and downstream or pericentral hypoxia. These dramatic changes in rates of alcohol metabolism and tissue concentrations of oxygen are not due to induced enzyme activity in liver. This phenomenon depends on activation of mitochondrial function, an increase in co-factor supply for nicotinamide adenine dinucleotide–dependent alcohol metabolism, depletion of glycogen reserves, liberation of fatty acids through activation of an adrenergic response to alcohol providing substrate for catalase, and activation of Kupffer cells, the hepatic resident macrophages responsible for production of cytokines and prostaglandins. An understanding of the mechanisms of hypermetabolism in liver can have vital ramifications for knowledge of both alcohol-related and alcohol-unrelated liver injury because hypoxia that is a result of hypermetabolism can compound effects of pharmaceuticals and environmental agents on the liver. Swift increase in alcohol metabolism is an excellent example of the complexity of cell–cell interactions in liver and extrahepatic regulation of biochemical and molecular events in this organ, and this important phenomenon shall be considered in studies of liver disease and biochemistry.

Keywords: Alcohol metabolism; Swift increase in alcohol metabolism; SIAM; Perfused liver; Hypermetabolism

1. Introduction

Chronic exposure to alcohol for up to 1 month leads to adaptive changes in both rodent and human liver and, among other pathologic effects, such as fatty liver, inflammation, and necrosis, results in an increase in alcohol metabolism and oxygen consumption (Mendelson & Mello, 1966; Videla & Israel, 1970). A series of publications in the 1970s highlighted the importance of increased co-factors available for the amplified oxygen demand of liver cells as a result of chronic (up to 14 to 30 days) exposure to alcohol as well as the concomitant increase in metabolism of alcohol. The swift increase in alcohol metabolism (SIAM) was discovered by using a large (5.0 g/kg, i.g.) acute dose of alcohol and was mechanistically explored by Thurman and co-workers by using the isolated perfused liver and in vivo models (Thurman et al., 1982; Yuki & Thurman, 1980).

Although it was known that prolonged alcohol feeding is required to stimulate alcohol metabolism in vivo, it was found that a 3-day dosing regimen is sufficient to increase the rate of metabolism about 1.5-fold (Bleyman & Thurman, 1979). This acute effect of alcohol was an early clue that an increase in rate of alcohol metabolism in vivo could be swift and was dose dependent. It is interesting that the ability for an increase in the rate of alcohol metabolism to occur in rats and mice is a heritable trait. Inbreeding of Sprague–Dawley rats led to the development of new strains that could be characterized as (1) SIAM-responsive, defined as an increase in the rate of metabolism after multiple exposures to alcohol, or (2) non-SIAM, in which the rate of metabolism did not change (Thurman, 1980). A comparison of inbred mouse lines also demonstrated a unique pattern of response to alcohol exposure, displaying a range from those that are slow to metabolize alcohol to those with a very rapid (up to threefold faster) response, depending on the dose of alcohol and time of exposure (Thurman et al., 1982). It was hypothesized that such a rapid increase in metabolism of alcohol after administration of high doses occurs, most
likely, because of the contribution of more than one pathway of alcohol metabolism. Further investigation of pathways responsible for the increase in alcohol metabolism in vivo after alcohol treatment implicated three major contributors: the mitochondria, the peroxisome, and endotoxin and Kupffer cell activation.

2. The role of mitochondria, glycogen, and glucose

The increased oxygen utilization by the mitochondria in the liver is a focal point in the phenomenon of SIAM. In 1980, the time course of the response of the perfused liver to a large dose of alcohol in the rat was first detailed (Yuki & Thurman, 1980). Results of this work demonstrated that in 2.5 h after acute (5 g/kg, i.g.) alcohol administration, as opposed to the findings obtained with chronic (30 day) feeding, a massive burst of hepatic respiration occurred, requiring high demand for oxygen and a near doubling of alcohol metabolism. The increase in metabolic demand of the liver after weeks of alcohol treatment is so great that an increase in the supply of oxygen is needed. Findings of studies with the use of isolated perfused liver after acute (5 g/kg, i.g.) alcohol treatment showed that an increase in the flow rate of oxygenated buffer is required to oxygenate the tissue adequately (Thurman & Scholz, 1976). It was subsequently demonstrated that hypoxia occurred in the downstream, oxygen-poor pericentral regions of the liver lobule after acute (5 g/kg, i.g.) and chronic (intragastric feeding for 30 days) alcohol treatment with the use of a hypoxia marker, pimonidazole (Arteel et al., 1996). It has been proposed that one of the primary links between SIAM and early alcohol-induced liver injury is the effect of prolonged hypoxia initiating the cascade of events causing oxidant stress. Treatment with alcohol causes multiple changes in the energetics of the liver by increasing oxygen demand and stimulating pathways of alcohol metabolism through supply of varied substrates.

It is important to note that the alterations in glycogen metabolism and glycolysis and their impact on increased mitochondrial respiration in SIAM are largely hormone mediated. This conclusion was based on several lines of evidence. It was first observed that thyroidectomy and administration of phentolamine markedly reduced, and adrenalectomy completely abolished, the hypermetabolic state produced in the liver of rats by chronic administration of alcohol (Bernstein et al., 1975). The effects produced by alcohol in the liver could also be reproduced by administration of a single large dose of epinephrine and were absent in thyroidectomized animals. The time course of alcohol treatment on hormone release in C57BL/6J mice after SIAM treatment was examined later in vivo (Forman et al., 1988). Levels of epinephrine, norepinephrine, corticosterone, and glucagon were positively correlated with rates of alcohol metabolism. Hormone levels increased overall about twofold to threefold beginning 30 min after alcohol administration and peaked at approximately the same time as the liver hypermetabolism peak observed in the perfused SIAM liver.

The mechanistic link among SIAM, hormonal regulation of energy supply, and the mitochondrial respiration was demonstrated by Yuki and Thurman (1980). Specifically, it was shown that alcohol treatment causes an adrenergic response that depletes glycogen and that SIAM does not occur in the fasted state. In studies with perfused liver, the SIAM response was blocked by adrenalectomy, adrenergic blockers (e.g., propranolol and phenoxybenzamine), hypophysectomy, or fasting, which depletes glycogen reserves. Administration of epinephrine instead of alcohol before perfusion produced a SIAM-like response in the perfused liver (Yuki et al., 1980). Blood glucose concentration was doubled and hepatic glycogen content was decreased about 40% to 50% at 2.5 h after alcohol treatment in vivo.

Alcohol inhibits glycolysis (as indexed by lactate and pyruvate release by the perfused liver) by inhibiting glyceraldehyde-3-phosphate dehydrogenase (Rawat & Lundquist, 1968), thereby diminishing ATP production. Thurman and Scholz (1977) further evaluated the role of alcohol on glycolysis. It was shown that at low alcohol concentrations (1.5 mM) glycolysis is diminished about 20%, which could account for a 5% to 10% elevation of respiration in perfused liver. In the case of a large dose of alcohol used to stimulate SIAM, glycolysis was decreased by 70%, and ADP crosses into the mitochondria by means of the adenine nucleotide translocator (ANT), making ADP available for increased rates of mitochondrial respiration and reoxidation of reduced form of nicotinamide adenine dinucleotide (NADH) and providing more oxidized form of nicotinamide adenine dinucleotide (NAD\(^+\)) for alcohol dehydrogenase (ADH)–dependent metabolism. The increase in oxygen uptake is blocked by the ANT inhibitor atractyloside, supporting the hypothesis that the effect of alcohol on hepatic respiration is regulated by ANT (Thurman & Scholz, 1977).

The effects of alcohol on the energy supply in liver are similar between species. Swift increase in alcohol metabolism was evaluated in human volunteers, and rates of alcohol metabolism were compared on two consecutive days. There was an increase in rate of about 40% in 20% of the population of male college students studied (Thurman et al., 1989), a phenomenon also that depends on a fed, not a fasted, state, as was shown in perfused liver. In a separate study by Crownover et al. (1986), when subjects were given alcohol followed 30 min later by a bolus dose of fructose, rates of alcohol metabolism increased on average by 25%. These results supported previous findings that fructose is metabolized to fructose-1-phosphate by means of fructokinase and that ATP is converted to ADP (Scholz & Nohl, 1976). The ADP is transported into the mitochondria where it stimulates oxygen uptake and reoxidation of NADH occurs, providing a co-factor supply for ADH-dependent alcohol metabolism.

Cytochrome P450s are important contributors to alcohol metabolism. There is little evidence of any contribution of P450s to increased oxygen uptake in SIAM. This conclusion
is based on the observation that changes in rates of alcohol metabolism in the perfused liver are not due to induced enzyme activity (Yuki & Thurman, 1980). Neither alcohol oxidation by the microsomal fraction nor hepatic ADH activity was altered by treatment with alcohol for 2.5 h, which led to the hypothesis that the increased rate of metabolism was due to increased co-factor supply.

3. The role of catalase and hydrogen peroxide supply

Findings of early work in isolated perfused rat liver demonstrated that chronic (35 to 49 days) alcohol treatment produced an increase in the rate of alcohol metabolism through both ADH-dependent and catalase-dependent pathways (Thurman & McKenna, 1975; Thurman et al., 1976). It was shown that rates of alcohol metabolism differ at low (7–12 mM; ADH dependent) versus high (25–35 mM; catalase dependent) concentrations of alcohol. In addition, when ADH was inhibited by using 4-methylpyrazole, an increase in supply of peroxide was produced after the addition of urate or glycolate, which generates hydrogen peroxide in liver, and rates of alcohol metabolism at high alcohol concentrations were increased. Results of these experiments demonstrated that catalase-dependent alcohol metabolism relies on substrate supply of hydrogen peroxide. Indeed, hepatic catalase activity is increased about 25% by chronic feeding of alcohol, and the increase in hydrogen peroxide supply is rate limiting and could not be ruled out for contributing to the adaptive increase because an increase in alcohol metabolism with the use of high concentrations of alcohol (25 mM) was partially blocked by the catalase inhibitor aminotriazole (Thurman et al., 1976).

The use of nonspecific inhibitors for in vivo studies often causes confusion and is the source of much scientific debate. Aminotriazole has been shown to inhibit cytochrome P450 2E1 (CYP2E1) as well as catalase. In addition, methylpyrazole has been shown to have effects on ADH-dependent and catalase-dependent pathways, making the above-mentioned results potentially uncertain with regard to specificity (Bradford et al., 1993a). To overcome these deficiencies, additional studies were performed. The experiments with the ADH-mutant deer mice were an early approach to evaluating involvement of catalase without the use of inhibitors. It was demonstrated that a large fraction of alcohol metabolism at high blood concentrations in ADH-positive and ADH-negative deer mice could be attributed to catalase (Bradford et al., 1993c). However, it was demonstrated that these deer mice lacked only hepatic ADH activity (Cronholm et al., 1992). Thus, this presented a dilemma in which the role for ADH was still not resolved unequivocally.

On the other hand, methanol is a selective substrate for catalase in rodents and makes quantitation of this metabolic pathway involvement possible. Methanol has been shown to be peroxidized by catalase–hydrogen peroxide at rates equivalent to alcohol (Chance, 2004), although it is not oxidized well by microsomal P450s (Teschke et al., 1975). Much of the early work with aminotriazole, which was subject to much debate, was repeated with the use of methanol alone. It was found that rates of oxygen uptake after alcohol or methanol treatment in vivo are identical in isolated perfused liver, supporting the suggestion that catalase plays an important role in SIAM (Bradford et al., 1999).

4. The role of endotoxin and Kupffer cells

Although a supply of fatty acids is required as substrate for catalase-dependent alcohol metabolism, the increase in ketogenesis seen with alcohol treatment was blocked by treatment with gadolinium chloride, a selective inhibitor of large hepatic macrophages, Kupffer cells (Bradford et al., 1993b, 1999). This finding demonstrated that not only one cell type or one pathway is required for SIAM. The ability of gadolinium chloride to selectively eliminate Kupffer cells in rat liver (Hardonk et al., 1992) sparked interest in the early 1990s in a previously overlooked cell type, a resident hepatic macrophage. The oxygen uptake measured in the perfused liver was shown also to be increased after liver transplantation, and the stimulation depends on the Kupffer cells (Qu et al., 1992).

Results of additional work demonstrated that Kupffer cells are activated by endotoxin and contain voltage-gated calcium channels (Ikejima et al., 1997). It was shown collectively that activation of Kupffer cells requires the presence of both endotoxin and intracellular calcium ions for release of cytotoxic substances, including eicosanoids, inflammatory cytokines, tumor necrosis factor-alpha, superoxide, and nitric oxide. It was demonstrated convincingly that SIAM could be mimicked by using endotoxin alone in vivo (Rivera et al., 1998). In addition, the antiendotoxin drug B-464 blocked SIAM and the increase in intracellular calcium required to activate Kupffer cells (Bradford et al., 1995).

Kupffer cells are important for activation of catalase-dependent alcohol metabolism, most likely by producing mediators such as prostaglandin E2 (PGE2) that may act through inhibition of lipoprotein lipase, which increase in supply of fatty acids to the liver, and increase in generation of hydrogen peroxide by means of peroxisomal beta-oxidation. Free fatty acid concentrations are elevated about 50% in plasma at 2.5 h after acute (5.0 g/kg, i.g.) alcohol treatment (unpublished observation, B. U. Bradford, 1994). In addition, treatment with oleate mimicked the effects of alcohol by causing a stimulation of catalase-dependent alcohol metabolism by increasing free fatty acid supply to peroxisomes. Treatment with indomethacin, an inhibitor of cyclooxygenase, resulted in abrogation of PGE2 production and also inhibited SIAM (Bradford et al., 1999).

An important link between PGE2 and peripheral lipoprotein lipase activity exists through the regulation of circulating free fatty acids for peroxisomal co-factors (Desancitis et al., 1994). In addition, PGE2 is known to stimulate cyclic
AMP-mediated (and adrenergic-mediated) mitochondrial hypermetabolism (Enomoto et al., 2000). It was later observed that PGE\(_2\) release by Kupffer cells in culture was blocked after isolation of Kupffer cells from rats treated with antibiotics, which destroy circulating endotoxin in the gut. These results support the hypothesis that Kupffer cells are activated by endotoxin, which is required for PGE\(_2\) production. Results of these studies filled in important gaps in the understanding of SIAM. The interconnected links among nutritional state, hormonal effects, cellular mediators such as cytokines, and co-factor supply are crucial in the understanding of this phenomenon.

5. Conclusions

In the 1980s, the working hypothesis for the mechanism of SIAM included the following steps: alcohol administration, causing an increase in adrenergic hormones, glycogen breakdown, and stimulation of glycolysis. Increased co-factor supply to the mitochondria accelerates oxygen uptake and alcohol metabolism. However, it seems that SIAM is a much more complex phenomenon, and the understanding of the biochemical and molecular events that are involved was significantly improved as a result of recent research (Fig. 1). We hypothesize that alcohol increases plasma endotoxin concentration, which activates Kupffer cells to produce mediators such as PGE\(_2\). In turn, this inhibits peripheral lipoprotein lipase, resulting in an increase in circulating free fatty acids and activation of mitochondrial respiration through cyclic AMP. Adrenergic stimulation by alcohol concurrently causes a release of free fatty acids from peripheral stores. Glycogen breakdown provides an increased supply of ADP to the mitochondria through glycolysis, and a burst of hepatic respiration increases co-factor supply of NAD\(^+\) for ADH-dependent alcohol metabolism. Free fatty acids are metabolized by acyl coenzyme A oxidase, which generates hydrogen peroxide for catalase-dependent alcohol metabolism in the peroxisome, and ADH-dependent alcohol metabolism occurs in the hepatocyte, a process that depends on concentration of alcohol in the cell and co-factor supply.

Hypermetabolism in general is applicable to other studies in addition to liver research. It is interesting that acute damage or injury in other tissues leads to a similar phenomenon that draws several mechanistic parallels with acute shifts in liver metabolism due to alcohol. For example, the response to injury or inflammation can cause a systemic inflammatory response syndrome (SIRS) in patients (Hill, 2000). This syndrome is characterized by a long period of hypermetabolism. In general terms, a cascade of events occurs, including hypoperfusion of tissue and hormone release, which stimulates hypermetabolism and resulting inflow of antiinflammatory and proinflammatory mediators.

**Fig. 1. Schema of working hypothesis for the mechanism of swift increase in alcohol metabolism (SIAM) in liver.** ACS = Acyl coenzyme A (CoA) synthetase; ADH = alcohol dehydrogenase; cAMP = cyclic AMP; CAT = catalase; EP-R = prostaglandin E\(_2\) receptors; LPL = lipoprotein lipase; NADH = reduced form of nicotinamide adenine dinucleotide; NAD\(^+\) = oxidized form of nicotinamide adenine dinucleotide; PGE\(_2\) = prostaglandin E\(_2\).
that work in concert to determine the outcome of the patient. Moreover, in burn-injured patients, the proinflammatory phase of recovery is often quite long (Jeschke et al., 2004). Overall, hepatic function seems to be an important predictor for patient survival in systemic disease or injury. In addition, the use of drug and nutritional interventions that target the liver is required for improved recovery and survival (Jeschke et al., 2004; Maher, 2002). Thus, the knowledge base on the events that occur in liver during acute alcohol-induced hypermetabolism may be applicable elsewhere.

Acknowledgments

Financial support for these studies was provided, in part, by grants from the National Institutes of Health: ES11391 and ES10126. Dr. Rusyn is a recipient of a Transition to Independent Position Award (ES11660).

References


