

LETTER TO THE EDITORS

ON INTRACELLULAR FORMATION OF ETHANOL AND ITS POSSIBLE ROLE IN ENERGY METABOLISM

ANATOLY G. ANTOSHECHKIN

Department of Analytical Biochemistry, Nulab, Inc., Los Angeles, CA 90039, USA

(Received 6 February 2001; in revised form 30 April 2001; accepted 11 June 2001)

Despite a great number of papers devoted to studies of the influence of alcohol on man's health, very few of them discuss the issue of the presence of ethanol in the human body not connected with alcohol consumption. Such ethanol is commonly called endogenous. It is believed to originate from the microbial fermentation of the carbohydrates in the gastro-intestinal tract (Krebs and Perkins, 1970; Blomstrand, 1971). Because of the low concentrations of endogenous ethanol, which reaches $0.39 \pm 0.45 \mu\text{g/ml}$ (0.039 mg/dl) in the blood of sober people (Jones *et al.*, 1983), as compared to concentrations produced by orally consumed exogenous ethanol, ethanol presence in the blood of abstaining people is not receiving any significant attention. This is understandable if endogenous ethanol is presumed to be synthesized by microbes. Such ethanol is not a truly endogenous substance of human cells, but enters them from the blood, as does ingested exogenous alcohol.

While acknowledging the synthesis of ethanol by intestinal flora, some researchers have considered the possibility of ethanol formation inside human tissues. These considerations were either theoretical by nature or were based on indirect and somewhat controversial data on ethanol concentration in the blood of so-called germ-free rats (Krebs and Perkins, 1970; Jones *et al.*, 1984). A scrupulous review of the literature concerning endogenous ethanol (Logan and Jones, 2000) described methodological difficulties of detection of endogenous ethanol in mammalian cells. It also pointed out the lack of pyruvate decarboxylase in man, which makes the conversion assumed by some authors of pyruvate into acetaldehyde in human cells impossible.

Therefore, the problem of ethanol synthesis inside human cells remains unresolved. On the one hand, there is a speculative belief that ethanol is an intracellular metabolite, while on the other hand, the absence of data confirming this argues against such a view. In addition, establishment of the fact that ethanol can be produced inside the cell and determination of its role in metabolism have paramount significance for our understanding of the mechanisms of action of exogenous alcohol. If a metabolic pathway in which ethanol is formed as an intermediate does exist in human cells, exogenous ethanol could primarily interfere in such a pathway. In this connection, it is interesting to review the data obtained in experiments aimed at determination of metabolites excreted by human fibroblasts during their cultivation *in vitro*. Using gas chromatography-mass spectrometry, excretion of pyroglutamic acid ethyl ester and palmitic acid hydroxyethyl ester has been demonstrated (Antoshechkin *et al.*, 1988 a,b). These data suggest the existence of intracellularly synthesized ethanol and its consequent biochemical interactions with some carboxylic acids.

The presence of alcohol dehydrogenase and aldehyde dehydrogenase in all cell types including neurons also argues

for an intracellular origin of ethanol. Existence of these enzymes in several isoenzyme forms of unequal distribution among different cellular compartments points to the presence of some oxidative processes that use ethanol and acetaldehyde as substrates. It is interesting to note that there are some data suggesting a possibility of reducing equivalents transfer through mitochondrial membrane by the ethanol \rightleftharpoons acetaldehyde redox shuttle (Grunnet, 1973). Taking this into account, together with the synthesis of ethyl esters of organic acids and their excretion from the cell, it is reasonable to suggest that ethanol synthesis is an intermediate step in the metabolic pathway of elimination of excess energy-releasing substrates from mitochondria. Some carboxylic acids, fatty acids in particular, are also energy-releasing substrates. Endogenous ethanol esterifies them, thus inactivating their carboxyl groups and facilitating their transport through membranes. Ethyl ester formation is probably carried out by glutathione S-transferases (Bora and Lange, 1993).

Although endogenous production of ethanol is relatively minute, further studies on its nature and effects may be of interest in understanding some of the actions of exogenous ethanol.

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