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Review Paper

Toxicology and Metabolic Effects of Methanol and Formaldehyde on the Brain, a Review Article

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ABSTRACT

Background: Methanol is a toxic alcohol for the human body. The molecular biology of methanol metabolites affecting different organs, such as the brain, is under investigation. This systematic review aimed to consider methanol toxic molecular biology, based on the original articles obtained from data banks to figure out recent achievements.

Methods: Scientific articles regarding the toxic effects and metabolites of methanol on the central nervous system (CNS) were collected from valid databases and classified based on their validity. Exclusion criteria were articles with duplicates, no available full text, review articles, case reports, and letters.

Results: Current metabolic reactions were addressed in the development of CNS diseases, such as optic neuropathy, basal ganglia lesions, and Alzheimer's disease. However, proteomic investigations introduced new metabolic changes, and serum proteins regarding blood coagulation, vitamin A metabolism, and immune responses were suggested for early detection of toxicity.

Conclusion: Besides CNS disorders introduced for methanol toxicity, there is no exact proteomic serum marker to diagnose toxicity soon; however, the interleukin-1 beta system is suggested as a candidate, and more investigation is required to improve its competency.

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1. Introduction

Methanol (Met) is the simplest type of alcohol with industrial application [1]. Met metabolites are formic acid (FC) and formaldehyde (FA), which may cause blindness and death [2]. The way of metabolizing toxic Met and FA accumulation in nerve tissue has attracted researchers› attention [3]. Met metabolites can cause complications in the central nervous system (CNS) with the possibility of dementia, Parkinson's disease (PA), and Alzheimer's disease (AD) [3]. Biomarkers of met toxicity could be extracted from body fluids. Proteomic technology investigates body proteins as a whole system and suggests new biomarkers regarding Met toxicity [4]. This review studied the molecular and metabolic changes in the human body following Met toxicity, according to the research achieved from data banks. Besides, some clinical health effects and biomarkers of Met toxicity on CNS were considered.

2. Materials and Methods

Databases, including Google Scholar, PubMed, and Scopus were searched with the set of keywords "methanol, toxicity, brain, metabolism, biomarker, protein" or a combination of individual words. English article selection was through title criteria at first, and the second criterion was abstract contents. The exclusion criteria were [1] review articles, guidelines, case reports, and letters, [2] articles without available data or full text, and [3] duplicate publications. We aimed to assess recent achievements regarding methanol intoxication in the human body. Two reviewers independently assessed the quality of the articles according to inclusion and exclusion criteria.

3. Results

We identified 329 title records from Google Scholar, PubMed, and Scopus; 225 articles screened as valuable and 104 articles were excluded. Also, 121 abstracts were assessed for eligibility and 83 articles were irrelevant and excluded. During the assessment of the found suitable 45 articles, another 11 articles were distinguished to be suitable and 55 articles were selected to study.

Kinetics and metabolism of methanol

Met is readily absorbed by all routes as inhalation, ingestion, and dermal exposure [5]. The primary site of Met metabolism is the liver. Met oxidizes to FA, and FC, and finally detoxifies to Co_2 [6]. Met is oxidized to FA by alcohol dehydrogenase (ADH1) in humans, by catalase in rats, or by a reaction of Met with hydroxyl radicals (non-enzymatic) in rats [7]. The FA oxidation product is formate (FO) as a conjugated base of FC. The FC concentration indicates Met toxicity and detoxification levels [8]. FC blocks the cytochrome C oxidase and could inhibit the mitochondrial respiratory chain, resulting in ATP depletion, lactate accumulation, and severe metabolic acidosis [9]. Two independent pathways generate (Figure 1) mediated by mitochondrial aldehyde dehydrogenase (ALDH22) or cytosolic ADH3 enzymes [10]. ADH3 or glutathione (GSH)-dependent FA dehydrogenase could oxidize FA to FO in two different reactions [11]. GSH reacts with FA without enzyme to form S-hydroxymethyl GSH, which is used to form S-formyl GSH as an ADH3 substrate [7]. Thiolase could hydrolyze S-formyl GHS to FO and GSH, catalyzed by ALDH2 in a single-step reaction [10]. Low concentrations of FA could be oxidized by AHD3 [12]. FO could continue to be oxidized to Co_2 in a metabolic pathway involving tetrahydrofolate (THF). FO at first is converted to 10-formyl THF, catalyzed by methylene tetrahydrofolate dehydrogenase (MTHFD1) in the cytosol or by mitochondrial isoform MTHFD1L [13]. 10-formyle THF is oxidized to Co_2 by ALDH1L1 (cytosolic) or ALDH1L2 (Mitochondrial) [14]. Both these two enzymes use cofactor $NADP^+$ to regenerate THF (Figure 1). Potential mechanisms involved in FA-stimulated GSH are related to the brain cells. Mechanisms involved in FA-induced accelerated GSH synthesis via Mrp1 from neural cell culture, are under investigation [15].

FC is a key toxicant metabolite. Un-dissociated FC can cross the blood-brain barrier (BBB) and lead to nervous system toxicity. Most of the metabolized Met is excreted as CO_2, but a small amount is excreted unchanged in urine or exhaled air [16].

Serum protein changes with methanol toxicity

Proteomics can investigate significant changes in proteins in the body as a system [4]. Increased blood coagulation proteins expressions such as von Willebrand factor, carboxypeptidase N, and alpha-2-antiplasmin and retinal binding protein associated with vitamin A metabolism, beside complement factors I, C3, and C5 associated with immune responses, apolipoprotein AI and AII, and adiponectin were reported in Met toxicity [17]. Neuroinflammation plays an important role in acute methanol toxicity of the brain. Elevated proinflammatory cytokines, such as IL-5 and IL-9, and anti-inflammatory cytokines, such as IL-4 and IL-10 were reported after

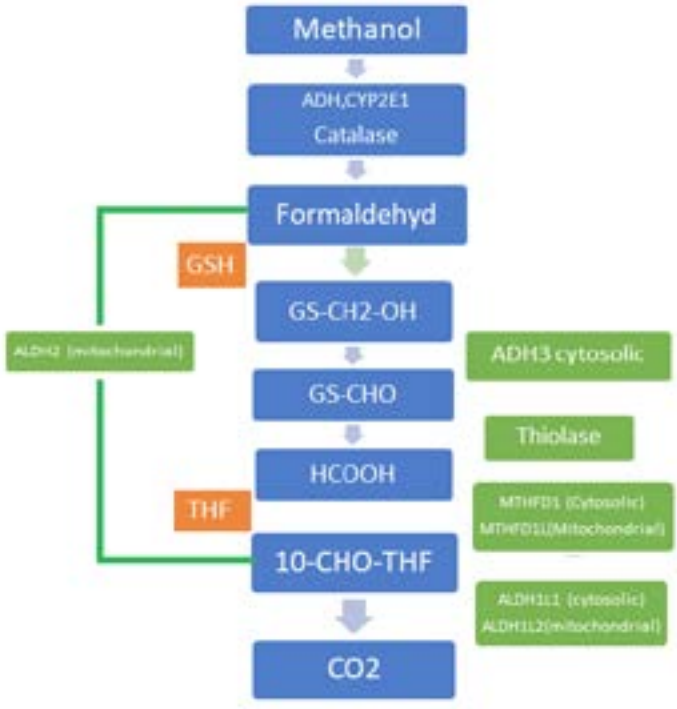

Figure 1. Methanol metabolism and formaldehyde disposal in cells

Abbreviations: ADH: Alcohol dehydrogenase; ADH3: GSH-dependent FA dehydrogenase; ALDH: Aldehyde dehydrogenase; GSH: Glutathione; MTHFD: Methylene tetrahydrofolate dehydrogenase; THF: Tetrahydrofolate.

two years of discharge from the hospital [18]. Biomarkers could assist in the early detection of Met poisoning.

Sources of Met for human exposure

Exogenous (EX) Met may be found in illegal alcoholic beverages [19] and also presents notably in fruits and vegetables. Inhalation of volatile Met-containing products also is significant [20]. Two sources have been suggested for endogenous (EN) Met. There is anaerobic fermentation by gut bacteria and some metabolic processes that transform S-adenyl methionine to Met [21] (Table 1). Met could be generated in the body by hydrolysis of protein carboxymethyl esters catalyzed by methylesterases [22].

Met & FA metabolism in nerve cells

Elevation of brain FA levels may cause neurodegenerative diseases [12]. Brain cell cultures, such as astrocytes and neurons encode semicarbazide-sensitive amine oxidases (SSAOs) and lysine-specific demethylase involved

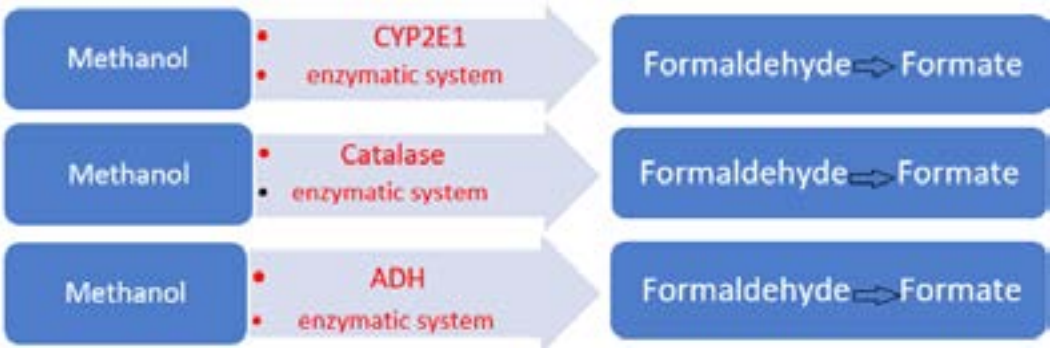

Figure 3. Three enzymatic systems related to methanol catabolism to acetaldehyde and formaldehyde

Table 1. Met sources and metabolites in summary (metabolites: FA & FO)

Row No.	Met Sources in the Body	Intermediate Compound	Last Compound	Results
1	Methionine	SAM, methyl acceptor	Endogenous Met	Metabolized by the liver, no hazard
2	Fruit & vegetables	Pectin/pectin methylesterases	Endogenous Met	Metabolized by the liver, no hazard
3	Aspartame & sweeteners	_	Endogenous Met	Metabolized by the liver, no hazard
4	Gut microflora	_	Endogenous Met	Metabolized by the liver, no hazard
5	Alcoholic beverages	Ethanol, methanol	Exogenous Met	Intoxication potential hazard

Abbreviations: FA: Formaldehyde, FO: Formic Acid; SAM: S-adenosyle-L-methionin.

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in FA metabolism. A key intermediate of sulfur amino acid metabolism is SAM, which is utilized by histone and DNA methyl transferase. Methionine and ATP substrates used by methionine adenosyltransferase (MAT) lead to the biosynthesis of SAM in rat brain cells [23]. Along with different sources of Met, SAM also participates in the pool of physiological Met formation [22]. Protein carboxymethylase is highly expressed in the mammalian brain and could be affected by SAM. Overmethylation of SAM has been shown to increase the formation of Met, FA, and FC in the striatum of rat brains [22]. SSAOs are located in the muscular layer and endothelium of brain vessels. SSAOs could catalyze the deamination of methylamine to FA, ammonia, and hydrogen peroxide. The major contribution of brain SSAOs to FA production was assessed in the SAMP8 mouse model of ADs [12]. Met and ethanol can pass through the BBB. However, the metabolic barrier function of ALDH and formaldehyde dehydrogenase (FDH) prevents the passage of FA and acetaldehyde across the BBB in rats [24]. ADH does not play a role in Met and ethanol metabolism in the brain. FDH in the human brain is likely involved in the oxidation of FA. Met and FA metabolic clearance occurs via two pathways. The first pathway follows the prevention of Met oxidation and FA formation in situ. Therefore, there is not any ADH1 activity in the brain and embryo. The second pathway is based on the oxidation of any FA synthesized in situ or introduced thr=ough BBB by FDH and ALDH2 enzymes in mitochondria [14].

Brain nuclei affected by Met metabolites

Met affects different nuclei and pathways in the brain depending on the density and duration of alcohol poisoning. Retinal ganglionic cell necrosis by Met causes oxidative stress acidosis (HCO_2) and mitochondria dysfunction leading to optic nerve neuropathy [25]. The basal ganglia (BG) is primarily responsible for motor control [26]. Met could generate reactive oxygen species (ROS) in BG to damage lipids, proteins, DNA, and cell death [27]. Met exposure causes a reduction in dopamine levels in the striatum [28] and the disruption of dopamine may contribute to motor and behavioral abnormalities [29] (Figure 2).

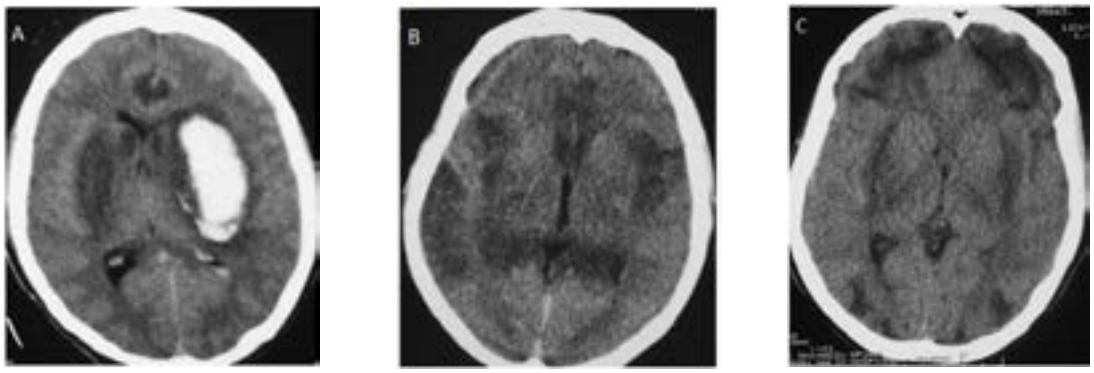

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Figure 2. CT scan images of methanol toxic brain showed bilateral hypodense lesions of the putamen and frontal lobe, left lenticular nucleus hemorrhage, and isolated white matter (A); Hypodense lesions in the insula and frontal lobes of the subcortical white matte (B); and bilateral putaminal hypodensities beside affected frontal and occipital white matter (C) [34].

Cerebellar cortical cells are damaged by Met intoxication [30]. Gait balance impairment was reported in survivors after intoxication with Met [31]. The increase of leukotrienes by Met involves glial cells and cerebellar cortical neuron damage, which induces coordinated movements of the cerebellum [32].

An increase in tau phosphorylated aggregation and amyloid-β (Aβ) plaques in brain lobes and hippocampus was reported regarding Met poisoning. Phosphorylation changes persist for six months in the brain after Met poisoning interruption, suggesting AD development following long-lasting and persistent pathological changes [3]. Met intoxication led to cerebral cortex edema and hemorrhagic necrosis of the thalamus and BG [33].

Met and FA relationship with Alzheimer's disease

Mitochondrial malfunction is associated with oxidative stress and neurodegenerative disorders, such as AD [35]. ALDH2 deficiency is suggested for AD pathogenesis [36]. ALDH2*2 is one of the major polymorphisms of ALDH2. ALDH2*2 homozygous allele does not have ALDH2 activity [37]. Accumulation of 4-hydroxy-2-nonenal (4-HNE) by low activity of ALDH2*2 was reported in AD and PA [38]. ALDH2*2 could increase the risk of AD in APOE-e4 homozygous [39].

Age causes dysregulation of FA metabolism in the brain. Excessive FA leads to impaired memory function by inhibiting NMDA receptors [40]. Excessive Aβ in ADs leads to FA accumulation by inactivation of ADH-5, and FA promotes Aβ oligomerization and fibrillation [41]. FA induces Aβ deposition in the extracellular matrix (ECM) of the deep cortex, leading to the blockage of dissolved drugs in matrix fluid to reach and treat injured neurons [42]. Phototherapy with near-infrared light could improve cognition in AD patients [43].

4. Discussion

An overview of current knowledge of the effects of Met sources and metabolites on the brain was considered in this review. Toxic Met could pass through three different metabolic pathways. The first pathway is the direct oxidation of Met by the action of catalase [44]. The second one is the production of hydroxyl radicals by H_2O_2, which in turn reacts spontaneously with Met to produce FA, and the third one is the ADH pathway [7] (Figure 3). The yield of the three reactions is FA, which is metabolized to FC in mitochondria by ADH2 action [44]. FA causes the accumulation of lactate and the emergence of metabolic acidosis and anion gap [45]. FA is converted to FC in the cytosol by FA dehydrogenase glutathione-dependent reactions [46]. FA as a neurotoxin can affect memory and neural behavior [47]. Elevation of FA levels and expression of enzymes related to FA formation are reported in AD and other neurological disorders, such as chorea and hemorrhage [48]. The retina, optic nerve, and BG are more affected depending on the concentration of Met poisoning [49]. Recently, proteomic studies introduced new serum biomarkers for Met toxicity, such as vitamin A key proteins, to inform us of other metabolic mechanisms besides oxidative injuries [4]. Von Willebrand factor and other coagulating proteins increase the coagulation tendency for methanol poisoning cases. Decreased interleukin-1 receptor accessory protein [50] suggested a new serum biomarker for acute methanol poisoning other than retinol-binding protein as a well-known candidate [17]. Pro-inflammatory and anti-inflammatory interleukin elevation is also suggested for brain injuries with Met [18]. According to animal research, Met and FA poisoning may lead to diseases, such as AD and PA. Finding biomarkers that reveal the initial stages of ethanol poisoning can be effective in the treatment and block the path of brain injuries.

Disturbances in energy metabolism and neurotransmitter systems, such as depletion of striatal dopamine and immune responses, are among the disturbances reported for BG poisoning by Met and FA [51]. Thus, the effects of Met toxicity on BG are complex and multifactorial. The molecular mechanisms and consequences depend on various factors, such as the dose of Met, duration of exposure to Met, and individual susceptibility [6]. Potential mechanisms involved in FA-stimulated GSH are rooted in brain cells. Glycolysis- and GSH-accelerated release by excess FA in brain cells may contribute to malfunction of cognitive performance and neurodegeneration, which leads to diseases, such as PA and AD [40]. Animal researches and aging researches showed that impaired energy metabolism and oxidative stress are related to increased FA in the brain, and the role of resveratrol is under investigation as an FA scavenger [52]. Aβ could inactivate ADH5 to accelerate FA accumulation in AD and FA promotes Aβ oligomerization, leading to fibrillation and tau hyperphosphorylation [53]. There is a vicious circle between Aβ assembly and FA generation. FA induces Aβ deposition in the ECM leading to deep cortex neuronal damage [54]. However, red-light phototherapy destroys Aβ deposition in the ECM as a suitable method, which needs more investigation [55].

5. Conclusion

Met acute toxicity effects on the CNS revealed that FA and FC may link to neurodegenerative diseases, such as AD and PA. Early detection of Met toxicity with the aid of suggested serum biomarkers could assist clinicians in the prevention of serious injuries. However, more investigations are required to improve the efficiency of new biomarkers.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics committee of Shahid Beheshti University of Medical Sciences (Code: IR.SBMU.RETECH.REC.1401.640).

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Authors' contributions

All authors equally contributed to preparing this article.

Conflict of interest

The authors declared no conflict of interests.

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