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REVIEW ARTICLE

Arsenic Exposure and Amyloid Precursor Protein Processing: A Focus on Alzheimer's Disease

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Abstract:

Background:

Arsenic is present in above permissible safe limits in groundwater, soil, and food, in various areas of the world. This is increasing exposure to humankind and affecting health in various ways. Alternation in cognition is one among them. Epidemiological research has reflected the impact of arsenic exposure on children in the form of diminished cognition.

Aims:

Considering this fact, the present study reviewed the impact of arsenic on amyloid precursor protein, which is known to cause one of the commonest cognitive disorders such as Alzheimer's disease.

Methods:

The present study reviews the arsenic role in the generation of amyloid-beta from its precursor that leads to Alzheimer's disease through the published article from Pubmed and Scopus.

Description:

According to the findings, regular, long-term exposure to arsenic beginning in infancy changes numerous arsenic level-regulating regions in the rat brain, which are related to cognitive impairments. Arsenic also affects the BBB clearance route by increasing RAGE expression. Arsenic triggers the proamyloidogenic pathway by increasing APP expression and subsequently, its processing by β-secretase and presenilin. Arsenic also affects mitochondrial dynamics, DNA repair pathway and epigenetic changes. The mechanism behind all these changes is explained in the present review article.

Conclusion:

A raised level of arsenic exposure affects the amyloid precursor protein, a factor for the early precipitation of Alzheimer's disease.

Keywords: Arsenic, Amyloid precursor protein, Alzheimer's disease, Arsenic biotransformation, Amyloid beta protein, CT region.

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1. INTRODUCTION

Amyloid precursor protein (APP) was initially cloned three decades ago, and a compelling case has been established over the years linking it to Alzheimer's disease (AD) which is the amassing of amyloid (Aβ) and the development of Aβ oligomers is considered to degrade synapses, likely contributing to the loss of memory and, eventually, dementia [1]. The APP family consists of SPTMP (type I) with short CT region and a significant ECD. APP along with APLPs include homologous regions throughout their ectodomains, particularly in their carboxy-terminal intracellular domains (containing the E1 and E2 domains) [2]. The APP gene is present on

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chromosome 21 in humans. Alternate splicing provides 8–11 APP protein isoforms with amino acid content (305, 639, 677, 695, 696, 714,733, 746, 751,752, 770) [3]. APP's cellular location changes over time. The secretory pathway transfers APP from the ER to the plasma membrane [4]. Arsenic trioxide (As_2O_3) is the most frequent inorganic arsenic in the atmosphere; nevertheless, it is certainly possible to identify it in groundwater, mud or foodstuffs, in addition to elemental arsenic (AsO3) or arsenites (AsO2) [5]. The accidental ingestion of arsenic is often inflicted by two main sources: work-related contact and contaminated beverages or liquor, and malevolent delivery [6]. APP processes post-translational alteration *via* two major pathways, including a variety of secretases and proteases. α- and γ-secretases cleave APP progressively throughout the non-amyloidogenic route [7]. One of the most perplexing challenges in study is the unknown physiological role of APP. The vast majority of research shows that APP overexpression improves cell health and proliferation [8]. AD is accompanied by the buildup of Aβ into amyloid plaques outside the cells and clusters of hyperphosphorylated tau protein within neurons [6]. These epigenetic adjustments are quite important in the complicated mechanism of action of As. Arsenic exposure alters microRNA gene expression, methylation of DNA, and enzymatic post-translational histone alteration [9]. The epigenome may be altered through exposure to heavy metals (arsenic, cadmium, nickel, mercury) and pollutants (dioxin, bisphenol A, benzene, diethylstilbestrol) [10]. This review focuses on the processing of APP expressions and epigenetic modifications produced by arsenic exposure in AD (Fig. **1**).

2. EXPOSURE OF ARSENIC TO THE HUMAN BODY

According to the toxicological evidence or hypotheses, arsenic ranks higher than other hazardous elements that reveal a potential for serious harm to the well-being of people. It has been demonstrated that these naturally formed metallic compounds at lower doses are hazardous, a co-carcinogen, as well as responsible for contributing to memory loss [11]. Currently, 10 µg/L is the arsenic limit for potable water [12, 13]. The pituitary gland has favorable arsenic content in the brain, specifically inorganic and dimethyl arsenicals [14]. The majority of human arsenic poisoning is prompted by rocks and soil discharging substances containing arsenic into groundwater [15].

Behavioral problems, learning difficulties, and changes in neurotransmission and receptors have all been related to iAs or their derivatives affecting fundamental cellular functions [16].

Even though the initiating hypothesis was primarily supported by epidemiologic studies linking older people's frequent contact with ecological iAs with declines in cognition. Research is piling up that the deteriorating brain function is considered a hallmark of AD that may share morphological as well as biochemical similarities with the potential exposure to iAs leading to a hazardous cascade [17, 18].

3. ENTRY AND BIOTRANSFORMATION OF ARSENIC IN ORGANISMS

Arsenic is found in the environment (groundwater, soils, atmosphere, and foodstuffs) largely in its elemental types (arsenite, arsenate) and is considered harmful [19]. Although the purpose of this article is to highlight the epigenetic perspective of APP processing and the detrimental impact of iAs and its breakdown products on animals, evaluating arsenic's physiochemical responses in mammalian and alternative biological processes could aid in the comprehension of how mammals cope with iAs [20]. For instance, in neutral pH aqueous conditions, iAsV is negatively charged as H_2AsO_4-/HAsO4^{2-} (pKa 6.9), which is identical to phosphate H2PO$_4$/HPO$_4^{2-}$, where it is taken up through phosphate channels among species like plants, microbes, and moulds [21, 22].

In vitro method of transfection suggests that utilising oocytes of *Xenopus laevis*, phosphate transporters are responsible for iAsV absorption. Among these investigated transporters, SLC34A2 is bound to iAsV with the highest specificity (*i.e*. rodents with a Km value of 50 M). Phosphate transporter inhibitors increased iAsV urine excretion, showing that iAsV is picked up by renal phosphate transport proteins [23, 24]. In contrast, the absorption rate of iAsV in human cells is considerably lower than that of iAsIII (arsenite), and utilizing arsenic *via* the phosphate channel seems to have some sort of function. Aquaporins/aquaglyceroporins appear to be exceptional iAsIII transporters into cells [25]. It is tempting to believe that iAsV resistance was implemented after iAsIII resistance because the primordial environment lacked oxygen, meaning that arsenic's oxidation state was trivalent [22]. The phosphorylation and acetylation of histones may be enhanced by iAsIII. It has been demonstrated that both iAsIII and MMAIII interact with enzymes involved in DNA repair by binding to cysteine residues in their zinc finger domain [26].

4. ARSENIC TOXICITY; MOLECULAR MECHANISM AND ITS IMPLICATIONS IN AD

Arsenic upon chronic administration has a major deleterious outcome, although the definitive etiology is still unknown. Several assumptions exist: One example is the creation of ROS, which attacks macromolecules like genetic material proteins, and fatty acids resulting in cellular injury [27]. Arsenic-induced DNA oxidation lowers the antioxidant potential and peptide thiols in rodent brain regions (brain cortex, striatum, hippocampus) with subsequent loss of ATP-synthase activity and LPO stimulation [28].

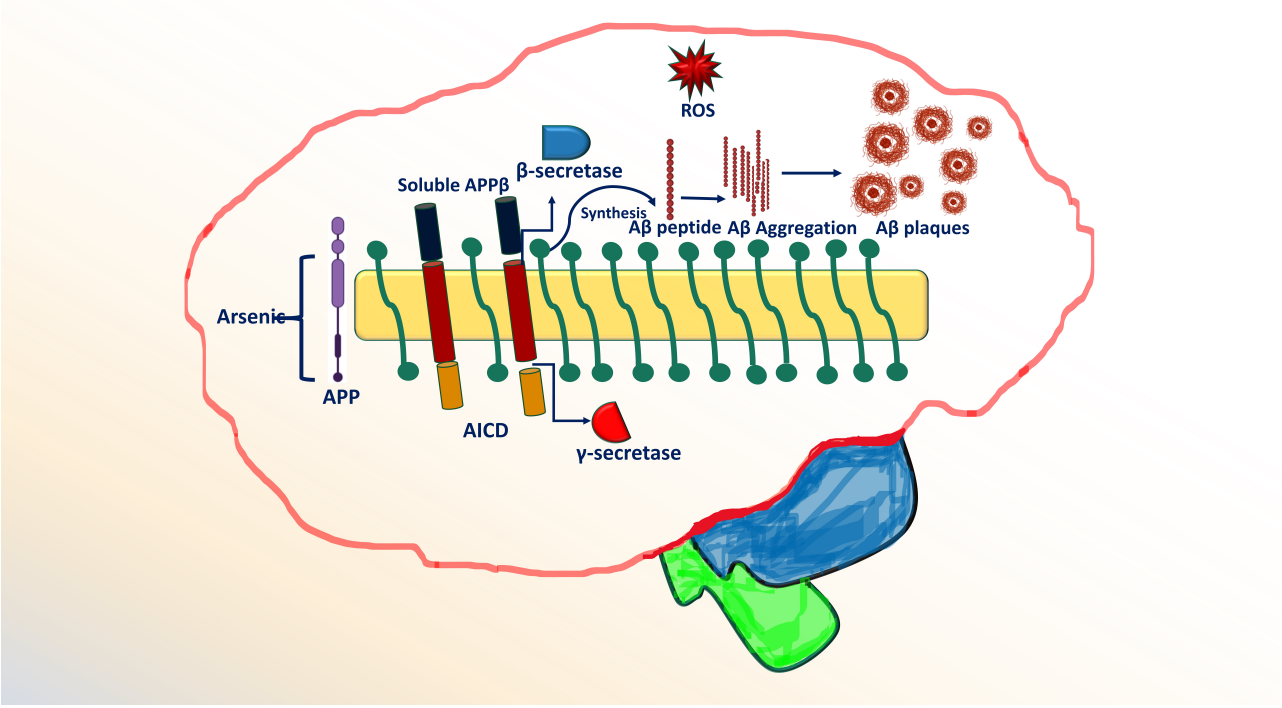

Fig. (1). Processing of APP with enzymes.

The pathobiology of a number of neurological diseases, including AD, relies largely on oxidative stress. Arsenic-induced neurological damage appears to be mainly caused by cytoplasmic release of ROS. The AMTs, which are involved with the formation of iAs in the vicinity of GSH, MMA and DMA [29], maybe a substrate for binding proteins in the brain. Inflammation forms a pathogenic triad with free radicals and faulty mitochondria [30]. Understanding the molecular processes underlying mitochondrial failure could aid in the development of more effective treatments for arsenic-mediated neurotoxicity. Multiple studies have demonstrated that arsenic-mediated neurotoxicity leads to mitochondrial dysfunction in the brain [31].

Arsenic has been shown to be mutagenic by interfering with the activity of mitochondria. As a result of the arsenic-induced impairment of mitochondrial oxidation, an abundance of superoxide anions was produced, which interacted with NO to simulate ONOO-(peroxynitrites) formation. Arsenic affects mitochondrial membrane function through the generation of ROS, destruction of DNA is linked to increased cell death by cytochrome C which starts off the cascading death process. As a result, mitochondria are the arsenic's primary neurotoxic target besides AD-related cognitive impairments [32, 33]. Apoptosis is a prevalent kind of cell death caused by arsenic poisoning. Arsenic-induced neurotoxicity has been linked to the triggering of JNK3 and p38MAPK pathways in cortical neurons. Recent research has shown that increasing Bax levels while decreasing Bcl-2 levels induces the loss of neuronal cells [34, 35]. Moreover, Fas/FasL is engaged in disruption to the epithelium triggered by arsenic *via* an exogenous apoptotic route, which is associated with changes in the NFkB and AP-1 signaling. Arsenic-induced neuronal degeneration encompasses the enhancement of autophagy-dependent mortality *via* stimulating AMPK while Akt suppression [36].

Arsenic-induced mitochondrial dysfunction reduces ATP generation, leading to ER stress, calcium (Ca^{2+}) accumulation in intracellular vesicles, and results insufficient Ca^{2+} signaling repair mechanisms. Triggered such as GSK-3a (PK molecule) [37] can produce memory problems or the hyperphosphorylation of tau when calcium signaling is altered.

5. AMYLOID PROTEIN PRECURSOR (EXPRESSION AND PROCESSING IN NORMAL AND HIGH ARSENIC LEVELS)

APP is processed post-translationally *via* two major pathways, including a variety of secretases and proteases. α- and γ-secretases process APP progressively along the non-amyloidogenic route [38]. APP processing can be either non-amyloidogenic progenitors that are fragmented off at amino acid 687 by the enzyme APP-α secretase or amyloidogenic, releasing the extracellular ectodomain and soluble APP (sAPP). Consequently, an APP-CTF83 remains in the plasma membrane. The cleavage of CTF83 by α-secretase leads to the release of short p3 segments and AICD into the cytoplasm [4]. (Figs. **2** and **3**)

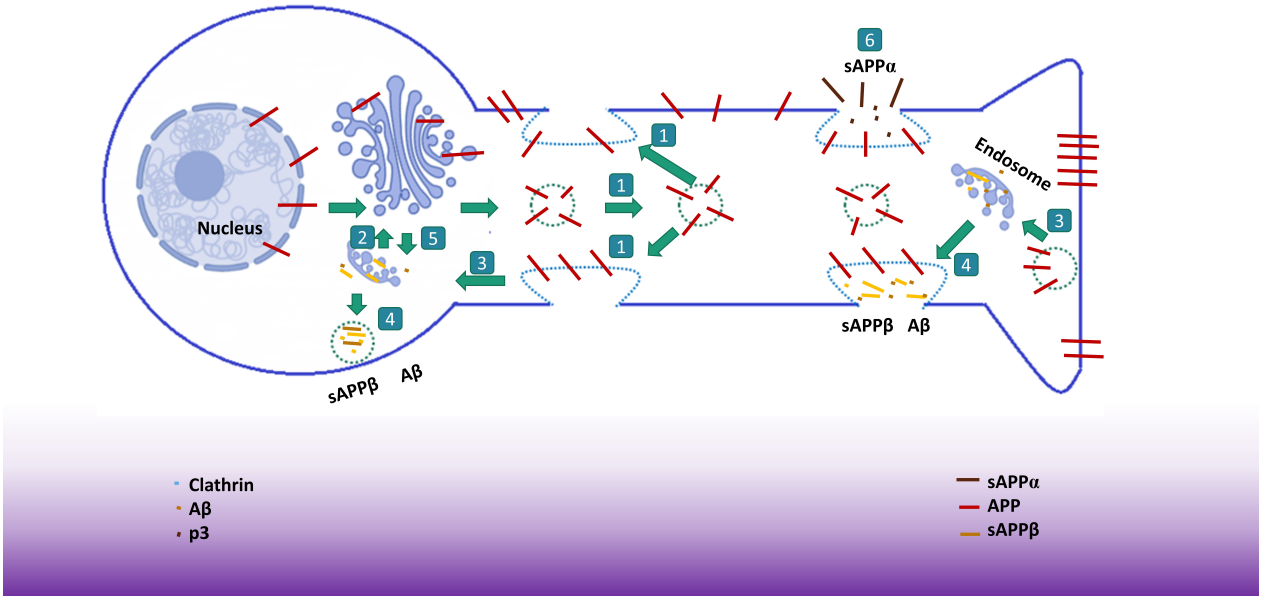

Fig. (2). Cellular processing of APP.

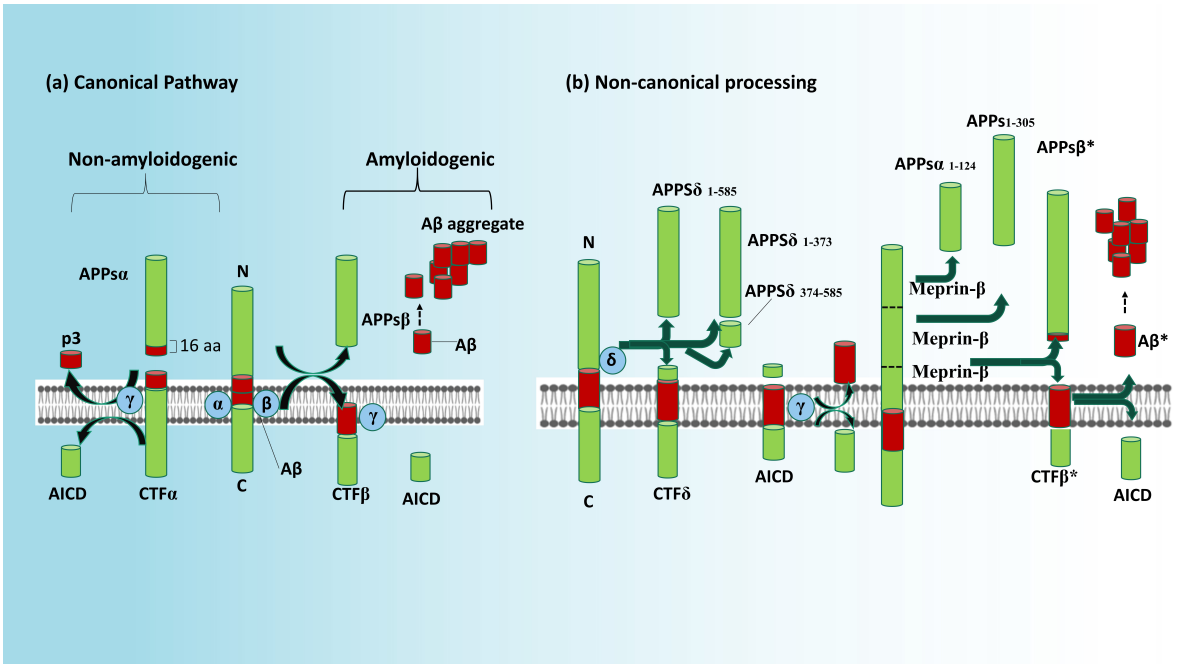

Fig. (3). Canonical and non-canonical pathway of APP processing.

According to a number of preclinical studies, As exposure enhances the processing and production of APP in mice. Sergio Zaraza and coworkers did preclinical studies on the processing of APP by *in vitro* SN56.B5.G4 cell line. They examined sodium arsenite and its metabolite activity (DMAA) on APP synthesis besides transduction in human APP Swedish mutation that expresses fundamental neurons. The results indicate suppression of cell survival and acetylcholinesterase and choline acetyltransferase activity that depends on both dosage and duration. Also, elevated amounts of the cell membrane and intracellular APP along with sAPP proportions have been observed [39].

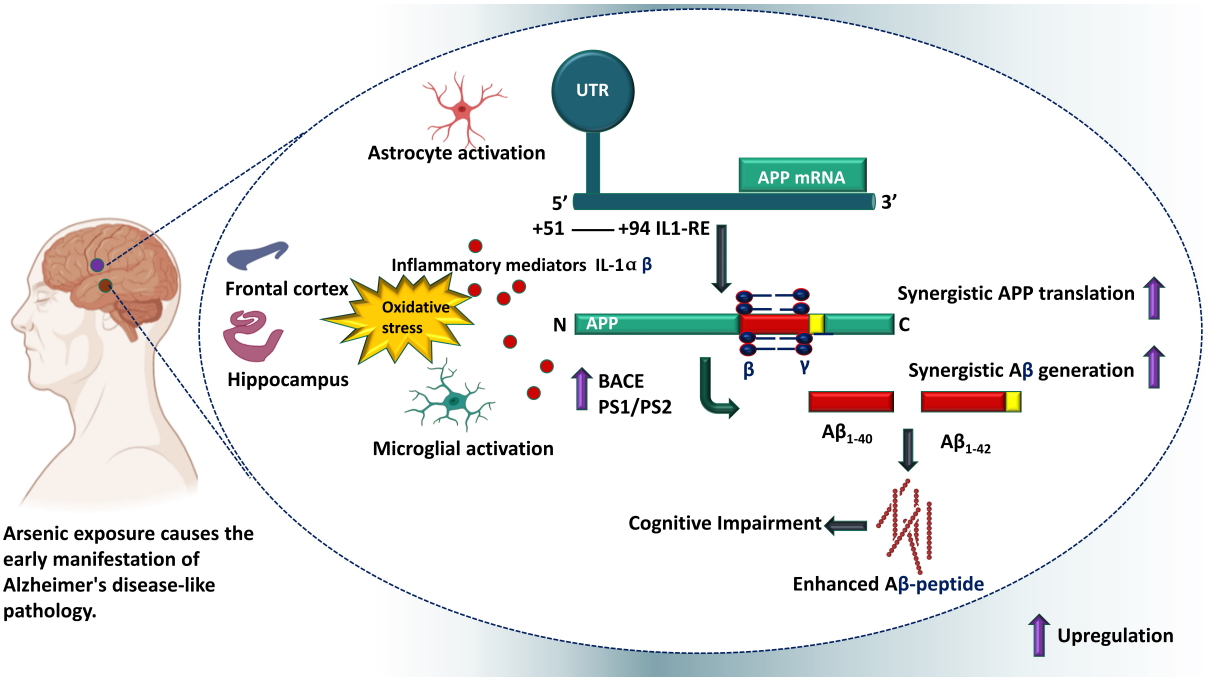

Fig. (4). Arsenic exposure and processing of APP.

Hydroarsenicism is a widespread health issue that has a global influence on the health of individuals. When iAs enter the body to which GSH has been infused undergo a methylation process *via* arsenic (III)-methyltransferase, resulting in the formation of dual toxic metabolites: monomethylated (MMAIII or V) and dimethylated (DMAIII or V) [40]. Although inorganic arsenic compounds or their metabolic products are removed by urine and faeces, a substantial amount of them accumulates in numerous organs, including the brain [41]. Furthermore, C. Escudero-Lourdes and co-researchers have acutely exposed rat cortical astrocytes to MMAIII, leading to microglial accumulation with no impairment of cell survival. The astrocytes with MMAIII reflect its LD50 of 10.52M, nevertheless, subtoxic concentrations (50-1000 nM) stimulated the expression of CoX-2, TNF-α, IL (1 and 6) besides MIF expression considerably. Upon treatment of MMAIII (50, 125, and 500nM), astrocytes demonstrated a significant increase in APP gene expression. This lines up to greater levels of expression of the BACE-1 protein [42]. Moreover, arsenic exposure may cause mental retardation, while inflammation may be a contributing factor. Another study was conducted on mummichogs (small killifish) to examine the effect of arsenic and the role of gender and age of exposure. Adult female and male mummichogs were subjected to different sodium arsenite doses (172 ppb, 575 ppb, 1720 ppb) for upto 10 days before spawning. The total number of eggs laid or the proportion that hatched was the same throughout each group. However, the group exposed to 1,720 ppb arsenic exhibited a considerable increase in abnormalities. Using total RNA extracted from adult liver tissue and 6-week-old juvenile liver tissue, custom-made microarrays were probed to determine changes in gene expression. Females exposed to 172 ppb and 575 ppb had 3% of their genes expressed differently in contrast with the placebo group. In males, each of the exposure groups comprised between 1% and 3% of the genes exhibiting different expressions. Various genes, particularly serum amyloid precursor and apolipoprotein expression get downregulated in a dose-dependent fashion while gender-independent [43]. In addition, qPCR was utilized to validate these regulatory patterns. These results clarify the gender-related consequences, dose, and frequency of arsenic response.

Atmospheric pollutants are potential causes of AD that mostly affect the elderly (Fig. **4**). As a result, investigation through research was executed to know early AD symptoms and pathogenesis produced by a combination of arsenic, lead, and cadmium that have all been associated with neurodegeneration. They injected cadmium, lead, and arsenic into rats at quantities seen in Indian groundwater, which were 0.098 ppm, 0.22 ppm, and 0.38 ppm, respectively each 10 times from the 5th day of development until the day after birth (day 180th). In the hippocampus and frontal cortex, a dose-dependent increase in Aβ was identified. During early adulthood, the impact was enormous and dosage that induced Aβ levels in animals that resembled levels observed in AD patients. The proamyloidogenic cascade was set off by metals through initiated APP overexpression with consequent processing of APP by β-secretase and presenilin. As per research, the process of Aβ creation initiates an increase in neuroinflammation. This promotes APP synthesis by targeting the 5'-untranslated domain of APP mRNA, which is particularly susceptible to cytokines [44]. The results demonstrate toxic metals like lead, arsenic and cadmium lead to APP processing and the early onset of AD-like pathogenesis. Sandra Aurora Nio *et al*. performed another study on chronic

arsenic exposure in the rat brain. The inorganic form of arsenic has a cumulative impact on a developing foetus, and infants up to 4 months of birth on Aβ synthesis with the eradication of it in Wistar rats being examined. The brains were collected after behavioural deficits caused by arsenic and expression of APP and RAGE was evaluated by western blot analysis; ELISA for analysis of Aβ production and BACE1 protein activity; and evaluating gene expression using RT-PCR, mass spectrometry of plasma and inductive coupling is determined. They found that chronic arsenic exposure induces behavioural abnormalities as well as elevated levels of soluble and membranous RAGE and a rise in Aβ cleavage. Moreover, the enzyme activity of BACE1 was also elevated. These results indicate that exposure to arsenic affects Aβ generation and RAGE-mediated amyloid elimination in an AD mouse model with behavioural changes [45]. This research gives credence to the idea that early metal exposure significantly contributes to neurotoxic amyloid buildup. Moreover, arsenic has been shown to possess negative impacts on myelination, namely in the cortex prefrontal region and corpus callosum. According to another study results, Wistar rats (males) were provided with water comprising 3 ppm sodium arsenite. The animals were treated from prenatal stages to the second, fourth, sixth, and twelve months of life. Immunohistochemistry and immunoblotting from the callosum and prefrontal cortex were used to determine the amounts of MBP. Mitochondrial mass or neurofilament phosphorylation and APP levels are two manifestations of damage to axonal cells that have been identified as potential demyelination-related alterations. At 12 months, there was a significant decrease in MBP levels in both regions, associated with the frontal region of the brain, revealing a drop in neuronal degeneration and a rise in mitochondrial density. Only the arsenic group demonstrated APP accumulation at 12 months of age and ultrastructural imaging revealed a reduction in white matter amount [46]. The ingestion of arsenic is believed to be linked with the buildup of APP. A recent study was conducted to explore gene expression alteration in participants chronically exposed to arsenic based on reports that reveal Bangladesh and portions of West Bengal have significant quantities (varying between 0.5 μg/L to 4600 μg/L) of arsenic contamination. The Bangladeshi 29 women with urine arsenic concentrations between 22.32 and 182812 μg/g creatinine were included in this investigation. RNA sequencing was used to examine RNA isolated from lymphocytes and monocytes in the peripheral blood. There exist 1,054 alleles statistically linked to heightened concentrations of arsenic in urine samples (FDR $p<0.05$), including 636 upregulated and 418 downregulated genes. In addition, ingenuity pathway analysis identified promising arsenic carcinogenesis target genes (EGR2, APP, DAPK1), microRNAs (210, 338, 155,) and NOTCH signaling [47]. These demonstrated by preclinical research that arsenic has a significant effect on APP accumulation, processing, and expression. Furthermore, these investigations clearly indicate APP as a potential arsenic carcinogenesis target gene, as well as arsenic exposure as a key contributor to neurotoxicity induced by amyloid buildup.

6. EPIGENETIC CHANGES RELATED TO ARSENIC EXPOSURE

The study of epigenetics emphasizes how external variables aside from modifications to the sequencing of DNA could impact biological and neuronal functions. The word “epigenetics” refers to the investigation of the gene regulation methods that turn genes on or off, as well as cellular interpretation of DNA being altered by factors outside of the cell's control. Therefore, research on epigenetics pursues to understand how the transcription propensity of a cell varies throughout time [48]. In the 1980s, it was revealed that inAs (indium arsenide) induces alterations in histone methylation as well as acetylation patterns in experimental cells of Melanogaster. This was the first indication of arsenic-mediated epigenetic modifications (methylation of the genomic DNA, irreversible posttranslational modifications to histone, and transcription of miRNA changes). Changes in these components can disrupt cellular homeostasis because each of these epigenetic components is essential for modulating gene expression [49, 50].

For instance, methylation of nucleic acid (DNA) is essential for optimal development and is involved in various steps, including transposon regulation [51]. 5-MeC originates from the methylation of cytosine's C'5 location known as CpG islands. Epigenetic modification has received the greatest attention [52] because it plays an essential role in the development of organisms. Methylation occurs in gene promoters and regions. This mechanism or process employs DNMTs (DNA methyltransferases), a class of enzymatic processes that modify DNA strands and SAM, a universal methyl contributor [53].

When the xenobiotic arsenic enters the bloodstream, it undergoes metabolic activation in the liver, where it is methylated, and subsequent reductive processes produce a number of methylated metabolites. The methyl donor for this detoxification process is provided by SAM. Arsenic exposure induces a deficiency of SAM in the body, which reduces DNMTs' function in regulating DNA methylation [12, 54]. After penetrating brain cells, iAs are methylated by a variety of mechanisms. Because iAsIII is always methylated, iAsV must be transformed to iAsIII before it can be used. Many brain regions express the AS3MT enzyme that methylates iAs [55].

The iAs exposure individually is not sufficient to cause neurodegeneration, as demonstrated by multiple investigations. On the other hand, certain iAs neurotoxicity can match or else collaborate with signaling pathways for neurodegenerative illnesses. Higher iA levels in urine have been linked to an elevated likelihood of AD [56]. Chronic iAs exposure induces behavioural impairments as well as higher levels of RAGE and BACE-1 expression in rats [57]. iAs perpetuates Aβ and Tau phosphorylation immunostaining in a modified AD rodent study, which is related to energy metabolism failure and changes in redox regulation [58]. Consequently, iAs increase cytokines expression in astrocytes, which correlates with enhanced levels of APP and BACE-1 [16]. iAs can work synergistically with dopamine to elicit neurotoxic events [31], which leads to α-synuclein accumulation [59]. The PS1 and BACE (β-secretase) genes were hypomethylated due to SAM

deficiency. This reduction in methyl elevated Aβ -producing BACE and PS1 proteins [49]. Additionally, the DNMT (1 and 3a) expression was reduced. In mice embryonic fibroblast cells, sodium arsenite inhibited HDAC p300, resulting in a reduction of H3K27ac at promoters. Su and colleagues established a DRC between total arsenic concentrations in European topsoil and the incidence and mortality of AD [45, 46]. Arsenite, an atmospheric toxin, induced a considerable elevation in the phosphorylation of numerous tau sites, particularly Thr (181,205 and 231), Ser (202, 262, 356, 396, 404) that matched with AD findings [60].

Another of the recognized approaches to histone modification, acetylation, has been correlated with arsenic. It affects the pyruvate dehydrogenase catalytic function that generates acetyl-CoA from pyruvate, a molecule crucial to histone acetylation to occur. Moreover, mice with exposition to arsenic during gestation identified hypoacetylation in H3K9 region, which is combined with a lack of perceptual and contextual cognition [61].

The work demonstrates that frequent, long-term exposure to arsenic throughout early childhood affects several arsenic-level regulatory sites in the rat brain. These alterations are associated with behavioural problems. In addition, exposure to arsenic affects the BBB clearing system by elevating RAGE expression. Arsenic generation is ultimately boosted by inorganic arsenic treatment by enhancing BACE1 activities and significantly elevating APP and RAGE in a mouse model devoid of AD predisposition. Furthermore, arsenic toxicity is an ecological issue that promotes memory problems and inadequate synaptic cleansing, lending credence to the notion that prenatal metal exposure may result in neurodegenerative disorders [57]. Post-translational histone modification enhances the DNA's availability for transcription thereby gene expression *via* modulating the architecture of chromatin. Histone methylation and demethylation turn genes “on” and “off,” respectively. The iAs decrease PDH activity, which catalyses the oxidation with acetyl-CoA formation from pyruvate. Reduced H3K9 acetylation leads to impairments in acute and chronic memory by iAs during pregnancy. In response to embryonic iAs exposure, a gender-dependent H3K9 modification (methylation and acetylation) is observed [61, 62].

CONCLUSION AND OUTLOOK

CNS is an especially vulnerable target for infectious agents (iAs). According to decades of research, iAs exposure changes the development of the neurological system. Given the ever-increasing AD incidence, the undesirable socioeconomic consequences of neurodegenerative disorders, and the steadily worsening pollutant levels in certain regions of the world, the evolving link between toxicant exposure and neurodegenerative disorders is of critical importance to public health. A few epidemiological studies have yielded inconclusive results in terms of obtaining significant estimates of AD hazard risk with crucial confounders, including repeated exposure to toxic substances, variation in genes, and environmental issues in chronic exposure cases. It happens due to limitations such as difficulties in precisely diagnosing AD cases and also due to a lack of specific biomarkers. The current knowledge on AD is focused not only on Aβ toxicity but also on evaluating the impact of non-amyloidogenic APP fragments. Energy impairment due to mitochondrial dysfunction is another area being studied widely for initiation events in AD, however, their link with APP metabolism is unclear. This strongly recommends that abnormal APP processing and Aβ peptide toxicity are essential for the development of AD in elderly individuals. Understanding the fragments of protein generated during proteolysis possess distinct physiological applications within the APP domain has made tremendous strides over the past several years. In this context, *in-vivo* methods employing genetically modified mice models have been highly efficient. Despite this, fundamental issues must still be addressed.

AUTHORS' CONTRIBUTIONS

Ravikant Sharma was involved in the conceptualization, writing of the manuscript and preparation of figure, Md. Abubakar and Priya Bisht contributed to manuscript writing and preparation of figures, Mahesh Rachamalla, Krishna Murti and V. Ravichandiran are involved in the manuscript review and input on critical points, Arun Kumar contributed to the mechanistic insight, manuscript review and input on critical points, Nitesh Kumar was involved in the conceptualization, manuscript writing, reviewing and conceptualization of figures.

LIST OF ABBREVIATIONS

5-MeC	=	5-methyl cytosine
AICD	=	APP intracellular domain
AMPK	=	Denosine monophosphate-activated protein kinase
AMTs	=	Arsenic methyl transferases
AP-1	=	Activator protein 1
AS3MT	=	Arsenic methyltransferase
BACE1	=	B-secretase 1 by enzymatic assay
BAX	=	Bcl-2-associated X protein
Bcl-2	=	B-cell lymphoma 2
COX2	=	Cyclooxygenase-2
CT	=	Cytoplasmic tail
CTF83	=	C-terminal subunit containing 83 amino acids
DMA	=	Dimethylarsinic acid
DMAA	=	Dimethylarsinic acid
ECD	=	Extracellular domain
ER	=	Endoplasmic reticulum
Fasl	=	Fas and Fas Ligand
GSH	=	Glutathionel
JNKs	=	C-Jun N-terminal kinases
LPO	=	Lipid peroxidation
MBP	=	Myelin basic protein
MMA	=	Monomethylarsonic acid
NF-κB	=	Nuclear factor kappa B
p38 MAPKs	=	P38 mitogen-activated protein kinases
PDH	=	Pyruvate dehydrogenase

PK	=	Protein Kinase
RAGE	=	Receptors for advanced glycation end products
ROS	=	Reactive oxygen species
SAM	=	S-adenosyl methionine
SLC34A2	=	Type IIb sodium-phosphate cotransporter
SPTMPs	=	Single-pass transmembrane protein
TNF-α	=	Tumour Necrosis Factor alpha

CONSENT FOR PUBLICATION

Not applicable.

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CONFLICT OF INTEREST

The authors declare no conflict of interest financial or otherwise.

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Declared none.

REFERENCES

[1] Chung, J.Y.; Yu, S.D.; Hong, Y.S. Environmental source of arsenic exposure. *J. Prev. Med. Public Health,* **2014**, *47*(5), 253-257. [http://dx.doi.org/10.3961/jpmph.14.036] [PMID: 25284196]

[2] Emadi, A.; Gore, S.D. Arsenic trioxide — An old drug rediscovered. *Blood Rev.,* **2010**, *24*(4-5), 191-199. [http://dx.doi.org/10.1016/j.blre.2010.04.001] [PMID: 20471733]

[3] Zhang, H.; Ma, Q.; Zhang, Y.; Xu, H. Proteolytic processing of Alzheimer's β□amyloid precursor protein. *J. Neurochem.,* **2012**, *120*(s1), 9-21. [http://dx.doi.org/10.1111/j.1471-4159.2011.07519.x]

[4] Singh, S. K.; Srivastav, S.; Yadav, A. K.; Srikrishna, S.; Perry, G. Overview of alzheimer's disease and some therapeutic approaches targeting Aβ by using several synthetic and herbal compounds. *Oxid Med Cell Longev,* **2016**, *2016*, 7361613. [http://dx.doi.org/10.1155/2016/7361613]

[5] Müller, U. C.; Deller, T.; Korte, M. Not just amyloid: physiological functions of the amyloid precursor protein family. *Nat. Rev. Neurosci,* **2017**, *185*(5), 281-298. [http://dx.doi.org/10.1038/nrn.2017.29]

[6] Matsui, T.; Ingelsson, M.; Fukumoto, H.; Ramasamy, K.; Kowa, H.; Frosch, M.P.; Irizarry, M.C.; Hyman, B.T. Expression of APP pathway mRNAs and proteins in Alzheimer's disease. *Brain Res.,* **2007**, *1161*, 116-123. [http://dx.doi.org/10.1016/j.brainres.2007.05.050] [PMID: 17586478]

[7] Haass, C.; Kaether, C.; Thinakaran, G.; Sisodia, S. Trafficking and proteolytic processing of APP. *Cold Spring Harb. Perspect. Med.,* **2012**, *2*(5), a006270. [http://dx.doi.org/10.1101/cshperspect.a006270] [PMID: 22553493]

[8] Kang, J. The precursor of Alzheimer's disease amyloid A4 protein resembles a cell-surface receptor *Nature,* **1987**, *325*(6106), 733-6. [http://dx.doi.org/10.1038/325733a0]

[9] Oh, E.S.; Savonenko, A.V.; King, J.F.; Fangmark Tucker, S.M.; Rudow, G.L.; Xu, G.; Borchelt, D.R.; Troncoso, J.C. Amyloid precursor protein increases cortical neuron size in transgenic mice. *Neurobiol. Aging,* **2009**, *30*(8), 1238-1244. [http://dx.doi.org/10.1016/j.neurobiolaging.2007.12.024] [PMID: 18304698]

[10] Hunter, S.; Brayne, C. Understanding the roles of mutations in the amyloid precursor protein in Alzheimer disease. *Mol. Psychiatry,* **2018**, *23*(1), 81-93. [http://dx.doi.org/10.1038/mp.2017.218] [PMID: 29112196]

[11] Jaishankar, M.; Tseten, T.; Anbalagan, N.; Mathew, B.B.; Beeregowda, K.N. Toxicity, mechanism and health effects of some heavy metals. *Interdiscip. Toxicol.,* **2014**, *7*(2), 60-72. [http://dx.doi.org/10.2478/intox-2014-0009] [PMID: 26109881]

[12] Bjørklund, G.; Aaseth, J.; Chirumbolo, S.; Urbina, M.A.; Uddin, R. Effects of arsenic toxicity beyond epigenetic modifications. *Environ. Geochem. Health,* **2018**, *40*(3), 955-965. [http://dx.doi.org/10.1007/s10653-017-9967-9] [PMID: 28484874]

[13] Sharavanan, V. J.; Sivaramakrishnan, M.; Sivarajasekar, N.; Senthilrani, N.; Kothandan, R.; Dhakal, N.; Sivamani, S.; Show, P. L.; Awual, M. R.; Naushad, M. Pollutants inducing epigenetic changes and diseases *Environ. Chem. Lett.,* **2019**, *18*, 325-343.

[14] Hughes, M.F.; Beck, B.D.; Chen, Y.; Lewis, A.S.; Thomas, D.J. Arsenic exposure and toxicology: a historical perspective. *Toxicol. Sci.,* **2011**, *123*(2), 305-332. [http://dx.doi.org/10.1093/toxsci/kfr184] [PMID: 21750349]

[15] Naujokas, M.F.; Anderson, B.; Ahsan, H.; Aposhian, H.V.; Graziano, J.H.; Thompson, C.; Suk, W.A. The broad scope of health effects from chronic arsenic exposure: update on a worldwide public health problem. *Environ. Health Perspect.,* **2013**, *121*(3), 295-302. [http://dx.doi.org/10.1289/ehp.1205875] [PMID: 23458756]

[16] Sánchez-Peña, L.C.; Petrosyan, P.; Morales, M.; González, N.B.; Gutiérrez-Ospina, G.; Del Razo, L.M.; Gonsebatt, M.E. Arsenic species, AS3MT amount, and AS3MT gen expression in different brain regions of mouse exposed to arsenite. *Environ. Res.,* **2010**, *110*(5), 428-434. [http://dx.doi.org/10.1016/j.envres.2010.01.007] [PMID: 20138265]

[17] Shankar, P.; Rayappan, J.B.B. Gas sensing mechanism of metal oxides: The role of ambient atmosphere, type of semiconductor and gases - A review. *Sci. Lett. J.,* **2015**, *4*, 126.

[18] Flora, S.J.S. Arsenic-induced oxidative stress and its reversibility. *Free Radic. Biol. Med.,* **2011**, *51*(2), 257-281. [http://dx.doi.org/10.1016/j.freeradbiomed.2011.04.008] [PMID: 21554949]

[19] Gong, G.; O'Bryant, S.E. The arsenic exposure hypothesis for Alzheimer disease. *Alzheimer Dis. Assoc. Disord.,* **2010**, *24*(4), 311-316. [http://dx.doi.org/10.1097/WAD.0b013e3181d71bc7] [PMID: 20473132]

[20] Bommarito, P.A.; Fry, R.C. Developmental windows of susceptibility to inorganic arsenic: a survey of current toxicologic and epidemiologic data. *Toxicol. Res. (Camb.),* **2016**, *5*(6), 1503-1511. [http://dx.doi.org/10.1039/C6TX00234J] [PMID: 29354260]

[21] Vaskenaposhian, H.; Zakharyan, R.A.; Avram, M.D.; Sampayo-Reyes, A.; Wollenberg, M.L. A review of the enzymology of arsenic metabolism and a new potential role of hydrogen peroxide in the detoxication of the trivalent arsenic species. *Toxicol. Appl. Pharmacol.,* **2004**, *198*(3), 327-335. [http://dx.doi.org/10.1016/j.taap.2003.10.027] [PMID: 15276412]

[22] Maciaszczyk-Dziubinska, E.; Wawrzycka, D.; Wysocki, R. Arsenic and antimony transporters in eukaryotes. *Int. J. Mol. Sci.,* **2012**, *13*(3), 3527-3548. [http://dx.doi.org/10.3390/ijms13033527] [PMID: 22489166]

[23] Przewłocki, R.; Przewłocka, B. Opioids in chronic pain. *Eur. J. Pharmacol.,* **2001**, *429*(1-3), 79-91. [http://dx.doi.org/10.1016/S0014-2999(01)01308-5] [PMID: 11698029]

[24] Yang, H-C.; Fu, H-L.; Lin, Y-F.; Rosen, B.P. *Metal Transporters*; Argüello, J.M.; Lutsenko, S.B.T.-C.T. Academic Press, **2012**, 69, pp. 325-358.

[25] Liu, Z.; Sanchez, M.A.; Jiang, X.; Boles, E.; Landfear, S.M.; Rosen, B.P. Mammalian glucose permease GLUT1 facilitates transport of arsenic trioxide and methylarsonous acid. *Biochem. Biophys. Res. Commun.,* **2006**, *351*(2), 424-430. [http://dx.doi.org/10.1016/j.bbrc.2006.10.054] [PMID: 17064664]

[26] Jiang, X.; McDermott, J.R.; Ajees, A.A.; Rosen, B.P.; Liu, Z. Trivalent arsenicals and glucose use different translocation pathways in mammalian GLUT1. *Metallomics,* **2010**, *2*(3), 211-219. [http://dx.doi.org/10.1039/B920471G] [PMID: 21069159]

[27] Holásková, I.; Elliott, M.; Hanson, M.L.; Schafer, R.; Barnett, J.B. Prenatal cadmium exposure produces persistent changes to thymus and spleen cell phenotypic repertoire as well as the acquired immune response. *Toxicol. Appl. Pharmacol.,* **2012**, *265*(2), 181-189. [http://dx.doi.org/10.1016/j.taap.2012.10.009] [PMID: 23088857]

[28] Csanaky, I.; Gregus, Z. Effect of phosphate transporter and methylation inhibitor drugs on the disposition of arsenate and arsenite

in rats. *Toxicol. Sci.,* **2001**, *63*(1), 29-36.
[http://dx.doi.org/10.1093/toxsci/63.1.29] [PMID: 11509741]

[29] Maciaszczyk-Dziubinska, E.; Migdal, I.; Migocka, M.; Bocer, T.; Wysocki, R. The yeast aquaglyceroporin Fps1p is a bidirectional arsenite channel. *FEBS Lett.,* **2010**, *584*(4), 726-732.
[http://dx.doi.org/10.1016/j.febslet.2009.12.027] [PMID: 20026328]

[30] Piątek, K.; Schwerdtle, T.; Hartwig, A.; Bal, W. Monomethylarsonous acid destroys a tetrathiolate zinc finger much more efficiently than inorganic arsenite: mechanistic considerations and consequences for DNA repair inhibition. *Chem. Res. Toxicol.,* **2008**, *21*(3), 600-606.
[http://dx.doi.org/10.1021/tx7003135] [PMID: 18220366]

[31] Rahman, M.; Hannan, M.; Uddin, M.; Rahman, M.; Rashid, M.; Kim, B. Exposure to environmental arsenic and emerging risk of Alzheimer's Disease: Perspective mechanisms, management strategy, and future directions. *Toxics,* **2021**, *9*(8), 188.
[http://dx.doi.org/10.3390/toxics9080188] [PMID: 34437506]

[32] Alboghobeish, S.; Pashmforosh, M.; Zeidooni, L.; Samimi, A.; Rezaei, M. High fat diet deteriorates the memory impairment induced by arsenic in mice: a sub chronic *in vivo* study. *Metab. Brain Dis.,* **2019**, *34*(6), 1595-1606.
[http://dx.doi.org/10.1007/s11011-019-00467-4] [PMID: 31422513]

[33] Rahman, M.A.; Rahman, M.D.H.; Biswas, P.; Hossain, M.S.; Islam, R.; Hannan, M.A.; Uddin, M.J.; Rhim, H. Potential therapeutic role of phytochemicals to mitigate mitochondrial dysfunctions in Alzheimer's Disease. *Antioxidants,* **2021**.
[PMID: 33379372]

[34] Prakash, C.; Soni, M.; Kumar, V. Mitochondrial oxidative stress and dysfunction in arsenic neurotoxicity: A review. *J. Appl. Toxicol.,* **2016**, *36*(2), 179-188.
[http://dx.doi.org/10.1002/jat.3256] [PMID: 26510484]

[35] Medda, N.; Patra, R.; Ghosh, T.K.; Maiti, S. Neurotoxic mechanism of arsenic: Synergistic effect of mitochondrial instability, oxidative stress, and hormonal-neurotransmitter impairment. *Biol. Trace Elem. Res.,* **2020**, *198*(1), 8-15.
[http://dx.doi.org/10.1007/s12011-020-02044-8] [PMID: 31939057]

[36] Liu, X.; Gao, Y.; Liu, Y.; Zhang, W.; Yang, Y.; Fu, X.; Sun, D.; Wang, J. Neuroglobin alleviates arsenic-induced neuronal damage. *Environ. Toxicol. Pharmacol.,* **2021**, *84*, 103604.
[http://dx.doi.org/10.1016/j.etap.2021.103604] [PMID: 33545379]

[37] Zhang, W.; Cui, X.; Gao, Y.; Sun, L.; Wang, J.; Yang, Y.; Liu, X.; Li, Y.; Guo, X.; Sun, D. Role of pigment epithelium-derived factor (PEDF) on arsenic-induced neuronal apoptosis. *Chemosphere,* **2019**, *215*, 925-931.
[http://dx.doi.org/10.1016/j.chemosphere.2018.10.100] [PMID: 30408888]

[38] Namgung, U.; Xia, Z. Arsenic induces apoptosis in rat cerebellar neurons *via* activation of JNK3 and p38 MAP kinases. *Toxicol. Appl. Pharmacol.,* **2001**, *174*(2), 130-138.
[http://dx.doi.org/10.1006/taap.2001.9200] [PMID: 11446828]

[39] Fu, S.C.; Lin, J.W.; Liu, J.M.; Liu, S.H.; Fang, K.M.; Su, C.C.; Hsu, R.J.; Wu, C.C.; Huang, C.F.; Lee, K.I.; Chen, Y.W. Arsenic induces autophagy-dependent apoptosis *via* Akt inactivation and AMPK activation signaling pathways leading to neuronal cell death. *Neurotoxicology,* **2021**, *85*, 133-144.
[http://dx.doi.org/10.1016/j.neuro.2021.05.008] [PMID: 34038756]

[40] King, A.P.; Wilson, J.J. Endoplasmic reticulum stress: an arising target for metal-based anticancer agents. *Chem. Soc. Rev.,* **2020**, *49*(22), 8113-8136.
[http://dx.doi.org/10.1039/D0CS00259C] [PMID: 32597908]

[41] Esch, F. S.; Keim, P. S.; Beattie, E. C.; Blacher, R. W.; Culwell, A. R.; Oltersdorf, T.; McClure, D.; Ward, P. J. Cleavage of amyloid beta peptide during constitutive processing of its precursor. *Science (80-.),* **1990**, *248*, 1122-1124.

[42] Zarazúa, S.; Bürger, S.; Delgado, J.M.; Jiménez-Capdeville, M.E.; Schliebs, R. Arsenic affects expression and processing of amyloid precursor protein (APP) in primary neuronal cells overexpressing the Swedish mutation of human APP. *Int. J. Dev. Neurosci.,* **2011**, *29*(4), 389-396.
[http://dx.doi.org/10.1016/j.ijdevneu.2011.03.004] [PMID: 21440049]

[43] Watanabe, T.; Hirano, S. Metabolism of arsenic and its toxicological relevance. *Arch. Toxicol.,* **2013**, *87*(6), 969-979.
[http://dx.doi.org/10.1007/s00204-012-0904-5] [PMID: 22811022]

[44] Leslie, E.M.; Haimeur, A.; Waalkes, M.P. Arsenic transport by the human multidrug resistance protein 1 (MRP1/ABCC1). Evidence that a tri-glutathione conjugate is required. *J. Biol. Chem.,* **2004**, *279*(31), 32700-32708.
[http://dx.doi.org/10.1074/jbc.M404912200] [PMID: 15161912]

[45] Escudero-Lourdes, C.; Uresti-Rivera, E.E.; Oliva-González, C.; Torres-Ramos, M.A.; Aguirre-Bañuelos, P.; Gandolfi, A.J. Cortical astrocytes acutely exposed to the monomethylarsonous acid (MMA^{III}) show increased pro-inflammatory cytokines gene expression that is consistent with APP and BACE-1: Over-expression. *Neurochem. Res.,* **2016**, *41*(10), 2559-2572.
[http://dx.doi.org/10.1007/s11064-016-1968-z] [PMID: 27321306]

[46] Niño, S.A.; Morales-Martínez, A.; Chi-Ahumada, E.; Carrizales, L.; Salgado-Delgado, R.; Pérez-Severiano, F.; Díaz-Cintra, S.; Jiménez-Capdeville, M.E.; Zarazúa, S. Arsenic exposure contributes to the bioenergetic damage in an Alzheimer's Disease Model. *ACS Chem. Neurosci.,* **2019**, *10*(1), 323-336.
[http://dx.doi.org/10.1021/acschemneuro.8b00278] [PMID: 30141907]

[47] Gonzalez, H.O.; Hu, J.; Gaworecki, K.M.; Roling, J.A.; Baldwin, W.S.; Gardea-Torresdey, J.L.; Bain, L.J. Dose-responsive gene expression changes in juvenile and adult mummichogs (Fundulus heteroclitus) after arsenic exposure. *Mar. Environ. Res.,* **2010**, *70*(2), 133-141.
[http://dx.doi.org/10.1016/j.marenvres.2010.04.003] [PMID: 20451245]

[48] Ashok, A.; Rai, N.K.; Tripathi, S.; Bandyopadhyay, S. Exposure to As-, Cd-, and Pb-mixture induces Aβ, amyloidogenic APP processing and cognitive impairments *via* oxidative stress-dependent neuroinflammation in young rats. *Toxicol. Sci.,* **2015**, *143*(1), 64-80.
[http://dx.doi.org/10.1093/toxsci/kfu208] [PMID: 25288670]

[49] Niño, S.A.; Martel-Gallegos, G.; Castro-Zavala, A.; Ortega-Berlanga, B.; Delgado, J.M.; Hernández-Mendoza, H.; Romero-Guzmán, E.; Ríos-Lugo, J.; Rosales-Mendoza, S.; Jiménez-Capdeville, M.E.; Zarazúa, S. Chronic arsenic exposure increases $A\beta_{(1-42)}$ production and receptor for advanced glycation end products expression in rat brain. *Chem. Res. Toxicol.,* **2018**, *31*(1), 13-21.
[http://dx.doi.org/10.1021/acs.chemrestox.7b00215] [PMID: 29155576]

[50] Niño, S.A.; Chi-Ahumada, E.; Ortíz, J.; Zarazua, S.; Concha, L.; Jiménez-Capdeville, M.E. *Toxicol. Appl. Pharmacol.,* **2020**, *393*

[51] Chen, Q.Y.; Shen, S.; Sun, H.; Wu, F.; Kluz, T.; Kibriya, M.G.; Chen, Y.; Ahsan, H.; Costa, M. *Environ. Pollut.,* **2020**, *259*

[52] Athanasopoulos, D.; Karagiannis, G.; Tsolaki, M. Recent findings in Alzheimer disease and nutrition focusing on epigenetics. *Adv. Nutr.,* **2016**, *7*(5), 917-927.
[http://dx.doi.org/10.3945/an.116.012229] [PMID: 27633107]

[53] Bailey, K.A.; Fry, R.C. Arsenic-associated changes to the epigenome: What are the functional consequences? *Curr. Environ. Health Rep.,* **2014**, *1*(1), 22-34.
[http://dx.doi.org/10.1007/s40572-013-0002-8] [PMID: 24860721]

[54] Aravin, A.A.; Sachidanandam, R.; Bourc'his, D.; Schaefer, C.; Pezic, D.; Toth, K.F.; Bestor, T.; Hannon, G.J. A piRNA pathway primed by individual transposons is linked to de novo DNA methylation in mice. *Mol. Cell,* **2008**, *31*(6), 785-799.
[http://dx.doi.org/10.1016/j.molcel.2008.09.003] [PMID: 18922463]

[55] Roy, R.V.; Son, Y.O.; Pratheeshkumar, P.; Wang, L.; Hitron, J.A.; Divya, S.P.; D, R.; Kim, D.; Yin, Y.; Zhang, Z.; Shi, X. Epigenetic targets of arsenic: emphasis on epigenetic modifications during carcinogenesis. *J. Environ. Pathol. Toxicol. Oncol.,* **2015**, *34*(1), 63-84.
[http://dx.doi.org/10.1615/JEnvironPatholToxicolOncol.2014012066] [PMID: 25746832]

[56] Reichard, J.F.; Puga, A. Effects of arsenic exposure on DNA methylation and epigenetic gene regulation. *Epigenomics,* **2010**, *2*(1), 87-104.
[http://dx.doi.org/10.2217/epi.09.45] [PMID: 20514360]

[57] Reichard, J.F.; Schnekenburger, M.; Puga, A. Long term low-dose arsenic exposure induces loss of DNA methylation. *Biochem. Biophys. Res. Commun.,* **2007**, *352*(1), 188-192.
[http://dx.doi.org/10.1016/j.bbrc.2006.11.001] [PMID: 17107663]

[58] Csanaky, I.; Németi, B.; Gregus, Z. Dose-dependent biotransformation of arsenite in rats—not S-adenosylmethionine depletion impairs arsenic methylation at high dose. *Toxicology,* **2003**, *183*(1-3), 77-91.
[http://dx.doi.org/10.1016/S0300-483X(02)00444-4] [PMID: 12504344]

[59] Yang, Y.W.; Liou, S.H.; Hsueh, Y.M.; Lyu, W.S.; Liu, C.S.; Liu, H.J.; Chung, M.C.; Hung, P.H.; Chung, C.J. Risk of Alzheimer's disease with metal concentrations in whole blood and urine: A case–control study using propensity score matching. *Toxicol. Appl. Pharmacol.,* **2018**, *356*, 8-14.
[http://dx.doi.org/10.1016/j.taap.2018.07.015] [PMID: 30025849]

[60] Chen, B.R.; Kozberg, M.G.; Bouchard, M.B.; Shaik, M.A.; Hillman,

E.M.C. A critical role for the vascular endothelium in functional neurovascular coupling in the brain. *J. Am. Heart Assoc.,* **2014**, *3*(3), 1-e000787.
[http://dx.doi.org/10.1161/JAHA.114.000787]

[61] Fuso, A.; Seminara, L.; Cavallaro, R.A.; D'Anselmi, F.; Scarpa, S. S-adenosylmethionine/homocysteine cycle alterations modify DNA methylation status with consequent deregulation of PS1 and BACE and beta-amyloid production. *Mol. Cell. Neurosci.,* **2005**, *28*(1), 195-204.
[http://dx.doi.org/10.1016/j.mcn.2004.09.007] [PMID: 15607954]

[62] Zhu, Y.; Li, Y.; Lou, D.; Gao, Y.; Yu, J.; Kong, D.; Zhang, Q.; Jia, Y.; Zhang, H.; Wang, Z. Sodium arsenite exposure inhibits histone acetyltransferase p300 for attenuating H3K27ac at enhancers in mouse embryonic fibroblast cells. *Toxicol. Appl. Pharmacol.,* **2018**, *357*, 70-79.
[http://dx.doi.org/10.1016/j.taap.2018.08.011] [PMID: 30130555]