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Subclinical Neurotoxicity of Mercury: A Behavioural, Molecular Mechanisms and Therapeutic Perspective

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ABSTRACT

This paper summarizes some recent research works performed during the last 20 years on the molecular mechanisms associated with mercury (Hg) effects on cognitive function. The study will provide a behavioral, molecular and therapeutic perspective from studies that suggest that mercury is neurotoxic metal with diverse effects on cellular functions in the brain. Mercury (Hg), and the organometallic compounds formed from it, are among the most toxic of substances to the global environment. Mercury exists in a wide variety of physical and chemical states, each of which has unique characteristics of target organ toxicity. Ultimately exposure to it can lead to neural destruction and degenerative disease, mercury vapor exposure from dental amalgam has been demonstrated to exceed the sum of all other exposure sources. Although mercury toxic potency is now widely known, its existence in the environment and in several man-made applications makes human exposure inevitable. There are many mechanisms that cause cellular destruction, that is why studies on different adverse mechanisms, and new methodological developments broaden the knowledge of the toxicity of this metal. For experiments on mercuric mercury, methyl mercury toxicity, several methods and cultures of different neural cell types were used. The study will also describe a non-pharmacological therapeutic approach, environmental enrichment, as promising strategy to reverse Hg effects on cognitive function.

Keywords: 1. Mercury (Hg),2: Methyl mercury, 3: Toxicity, 4: Mercury vapor, 5: Neurotoxic

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INTRODUCTION

Mercury is an element in the earth's crust. Pure mercury is a liquid metal, sometimes referred to as quicksilver that volatizes readily. It has traditionally been used to make products like thermometers, switches, and some light bulbs. Mercury is one of the most toxic elements on the planet, probably second only to plutonium, yet worldwide people have it in all tissues of their bodies, and it continues to be dumped into our waterways and soil, placed into our teeth, and injected into our bodies. Mercury exists in a wide variety of physical and chemical states, each of which associated with exposure to elemental mercury vapor (Hg0) and methyl mercury (CH3Hg+; MeHg) involve the central nervous system (CNS), while the kidney is the target organ for the mono- and divalent salts of mercury (Hg^{+} and Hg^{++}, respectively), Aschner and Aschner [1]. Mercury is environmentally ubiquitous, and both wildlife and humans are exposed to the toxic effects of its environmental residues. Mercury is found both naturally and as an introduced contaminant in the environment, Marek [2]. Although its potential for toxicity in highly contaminated areas such as Minamata Bay, Japan, in the 1950's and 1960's, is well documented, research has shown that mercury can be a threat to the health of people and wildlife in many environments that are not obviously polluted. The risk is determined by the likelihood of exposure, the form of mercury present (some forms are more toxic than others), and the geochemical and ecological factors that influence how mercury moves and changes form in the environment [2-4].

EXPERIMENTAL PROCEDURE

A narrative review of studies on mercury, the organometallic compounds formed from it and mercury-containing compounds are presented to illustrate the information currently available on occurrence in the environment and neurotoxicity of mercury [5,6, 9,11]. The study of mercury neurotoxicity usually include a common tests such as test hair samples, tests on samples of skin, nails, stool or feces, breast milk and the best and the only truly accurate and definitive test for mercury levels and possible mercury poisoning is a blood sample [12,13,16]. The studies were reviewed in more depth in order to get more understanding of mercury neurotoxicity and the behavioral, molecular and therapeutic perspective.

RESULTS AND DISCUSSION

The diagnostic approach for patients with suspected mercury toxicity begins with a thorough history that includes occupations, hobbies, and levels of seafood intake. All toxic presentations, whether acute, chronic, or subacute, are difficult diagnoses because multiple organ systems are affected (eg, CNS, kidney, mucous membranes) and can mimic a variety of other diseases [7,8,14]. The clinical presentation of mercury neurotoxicity can manifest in a variety of ways, depending on the nature of the exposure, the intensity of the exposure, and the chemical form, Bolger [19].

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Elemental mercury

Elemental mercury (Hg) is found in liquid form, which easily vaporizes at room temperature and is well absorbed (80%) through inhalation. Table 1 summarizes the clinical toxicologic features of mercury vapor and inorganic mercury, Gossel and Bricker [12].

Table 1: The Major Clinical Toxicologic Features of Mercury.

The Major Clinical Toxicologic Features of Mercury.		
Variable	**Mercury Vapor**	**Inorganic Divalent Mercury**
Common Route of Exposure	Inhalation	Oral
Principal Target Organ	Brain, peripheral nerves, kidneys	Kidney
LOCAL SYMPTOMS		
Lung	Bronchitis, pneumonitis(>1,000 mcg/M3 air)	
Digestive Tract	Metallic taste, stomatitis, gingivitis, increased salivation (>1,000 mcg/M3 air)	Metallic taste, stomatitis, gastroenteritis
Skin		Hives, blisters
SYSTEMIC SYMPTOMS		
Kidney	Proteinuria	Proteinuria, tubular necrosis
Nervous system	Peripheral neuropathy(>500 mcg/M3 air)	Painful, pink extremities (Acrodynia)
Brain	Irritability, tremor (>500 mcg/M3 air)	
Half-time without treatment	60 days in body	40 days in body
Treatment	DMSA by mouth	DMSA by mouth

Its lipid-soluble property allows for easy passage through the alveoli into the bloodstream and red blood cells (RBCs). Once inhaled, elemental mercury is mostly converted to an inorganic divalent or mercuric form by catalase in the erythrocytes [19,20].

This inorganic form has similar properties to inorganic mercury (eg, poor lipid solubility, limited permeability to the blood-brain barrier, and excretion in feces). Small amounts of nonoxidized elemental mercury continue to persist and account for central nervous system toxicity, Thomas [16] . Inorganic mercury, found mostly in the mercuric salt form (eg, batteries), is highly toxic and corrosive. It gains access to the body orally or dermally and is absorbed at a rate of 10% of that ingested. It has a nonuniform mode of distribution secondary to poor lipid solubility and accumulates mostly in the kidney, causing significant renal damage. Although poor lipid solubility characteristics limit CNS penetration, slow elimination and chronic exposure allow for significant CNS accumulation of mercuric ions and subsequent toxicity. Long-term dermal exposure to inorganic mercury may also lead to toxicity. Excretion of inorganic mercury, as with organic mercury, is mostly through feces. Renal excretion of mercury is considered insufficient and attributes to its chronic exposure and accumulation within the brain, causing CNS effects [18,20].

Inorganic mercury as both mercuric and mercurous salts was also the chief cause of acrodynia, a childhood disease that is now mainly of historical interest. The clinical symptoms of acrodynia consist of painful, red, swollen fingers and toes in association with photophobia, irritability, asthenia, and hypertension. It is believed to be a hypersensitivity reaction [16,18].

Mercury from dental amalgams

Dental amalgams have been in use for over 150 years. They are inexpensive and thought to be more durable and easier to use than other types of fillings. The amalgam consists of approximately 50 percent mercury combined with other metals such as silver and copper, Skare [4]. Since their introduction, dental amalgams have been a source of controversy because of the assumed health risks of mercury. The arguments between the protagonists and antagonists have been referred to as the "amalgam wars" and became more heated around 1970 with the discovery that amalgams can release mercury vapor into the oral cavity in concentrations that are higher than those deemed safe by occupational health guidelines. Subsequently, it was realized that the actual inhaled dose was small, owing to the small volume of the oral cavity. Nevertheless, amalgam fillings are the chief source of exposure to mercury vapor in the general population. Brain, blood, and urinary concentrations correlate with the number of amalgam surfaces present. It has been estimated that 10 amalgam surfaces would raise urinary concentrations by 1 µg of mercury per liter, roughly doubling the back ground concentrations. Higher urinary concentrations are found in persons who chew a great deal. For example, the long-term use of nicotine chewing gum will raise urinary concentrations close to occupational health limits [4,13,23].

The removal of amalgam fillings can also cause temporary elevations in blood concentrations, since the process transiently increases the amount of mercury vapor inhaled. Cases of poisoning from inhalation of mercury vapor have been recognized for centuries, Gossel and Bricker [12]. Severe cases are characterized by a triad of intentional tremor, gingivitis, and erethism (Table 1).

The Food and Drug Administration (FDA) consumer update on dental amalgam advises, as a precaution, that pregnant women and persons who may have a health condition that makes them more sensitive to mercury exposure should discuss dental treatment options with their health care practitioner. FDA, which regulates the use of dental amalgam, is currently reviewing the scientific evidence on the safe use of amalgam [13,15]. Amalgam use is declining because the incidence of dental decay is decreasing and because improved substitute materials are now available for certain applications. If dental patients do not want to use mercury amalgam, there are several non-mercury restorative materials available. Presently, there are many types of restorative materials such as resin composite, glass ionomer, resin ionomer, porcelain, and gold alloys. Each type of restorative material has advantages and disadvantages. Some factors that influence the choice of restorative material used include: cost, strength, durability, location of cavity, and aesthetics [10,15].

Mercury from quicksilver in the home

Spills of liquid mercury in the home carry a risk of vapor inhalation. Quicksilver is an attractive play object for children and is found in many homes, especially in developing countries. High levels of exposure to mercury vapor can result from the cultural and religious use of elemental mercury, including sprinkling mercury on the floor of a home or car, burning it in a candle, and mixing it with perfume, Gibson [24]. Infants and young children, whose breathing zones are closest to the floor, are at highest risk, since mercury vapor is heavy and tends to form layers close to the floor. Ingested liquid mercury passes through the gastrointestinal tract essentially unabsorbed. Centuries ago a tablespoonful of quicksilver was used to treat constipation [24,25].

Alkyl mercury

Organic mercury can be found in 3 forms, aryl and short- and long-chain alkyl compounds. Organic mercurials are absorbed more completely from the GI tract than inorganic salts are; this is because of intrinsic properties, such as lipid solubility and mild corrosiveness (although much less corrosive than inorganic mercury), Grandjean [10]. Once absorbed, the aryl and long-chain alkyl compounds are converted to their inorganic forms and possess similar toxic properties to inorganic mercury. The short-chain alkyl mercurials are readily absorbed in the GI tract (90-95%) and remain stable in their initial forms. Alkyl organic mercury has high lipid solubility and is distributed uniformly throughout the body, accumulating in the brain, kidney, liver, hair, and skin. Organic mercurials also cross the blood-brain barrier and placenta and penetrate erythrocytes, attributing to neurological symptoms, teratogenic effects, and high blood to plasma ratio, respectively [10,11,22].

Among humans, the sole source of exposure to methyl mercury is the consumption of fish and sea mammals. Methyl mercury is produced environmentally by biomethylation of the inorganic mercury present in aquatic sediments. It accumulates in the aquatic food chain and reaches its highest concentrations in long-lived, predatory fish such as swordfish and shark in the oceans and pike and bass in fresh water. Concentrations of mercury in ambient air and water are too low to pose a serious risk to the general population. The brain is the primary target tissue. Adults present with paresthesias of the circumoral area and hands and feet, followed by visual-field constriction and ataxia. Neuropathological examination reveals regional destruction of neurons in the visual cortex and cerebellar granule cells, Thomas [16]. There is usually a latent period of weeks or months between exposure and the onset of symptoms. Methyl mercury has a high affinity for sulfhydryl groups, which attributes to its effect on enzyme dysfunction. One enzyme that is inhibited is choline acetyl transferase, which is involved in the final step of acetylcholine production. This inhibition may lead to acetylcholine deficiency, contributing to the signs and symptoms of motor dysfunction, Steuerwald [11].

Excretion of alkyl mercury occurs mostly in the form of feces (90%), secondary to significant enterohepatic circulation. The biological half-life of methyl mercury is approximately

65 days. Organic mercury is found most commonly in antiseptics, fungicides, and industrial run-off. Table 2 summarizes the clinical toxicologic features of methyl mercury and ethyl mercury, Gossel and Bricker [12].

Table 2: The Major Clinical Toxicologic Features of Methyl and Ethyl mercury.

The Major Clinical Toxicologic Features of Methyl and Ethyl mercury		
Variable	Methyl Mercury	Ethyl Mercury
Common Route of Exposure	Oral (eating fish)	Parenteral (preservative in vaccines)
Principal Target Organ	Brain	Brain, kidney
SYSTEMIC SYMPTOMS		
Kidney		Proteinuria
Nervous system		Painful, pink extremities (Acrodynia)
Brain	Abnormal sensations, Loss of balance, visual and hearing loss (>200 mcg/L blood)	Abnormal sensations, Loss of balance, visual and hearing loss
Half-time in the body without treatment	70 days	20 days
Treatment	DMSA by mouth, but chelators do not reverse damage	DMSA by mouth, but chelators do not reverse damage

In United States, the 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System documented about 2400 single exposures to mercury or compounds containing mercury.1 of these, 305 were in children younger than 6 years and 983 were in persons older than 19 years. Overall, 45 individuals were reported to have moderate effects, 3 had major effects, and none died as a result of mercury exposure, Alvin [26].

Mercury-containing compounds

Thimerosal is a mercury-containing preservative used in some vaccines and other products since the 1930s. No harmful effects have been reported from thimerosal at doses used in vaccines, except for minor reactions like redness and swelling at the injection site. However, in July 1999, the Public Health Service (PHS) agencies, the American Academy of Pediatrics (AAP), and vaccine manufacturers agreed that thimerosal should be reduced or eliminated in vaccines as a precautionary measure. Today, with the exception of some influenza vaccines, none of the vaccines used in the United States to protect preschool children against 12 infectious diseases contain thimerosal as a preservative, Clarkson [20]. In 2004, Immunization Safety Review Committee of the IOM shifted from the position of neutrality to the conclusion that "the evidence favors rejection of a causal relationship between thimerosal-containing vaccines and autism." Since 2004, two cohort studies from the United Kingdom examined the relationship between thimerosal contained within vaccines and autism, and their conclusions were in agreement with the IOM that there is no casual relationship between the two [20,27].

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SYMPTOMS OF MERCURY POISONING IN HUMANS

The first symptom is psychological disturbances such as angry fits, short term memory loss, low self esteem, inability to sleep, loss of self-control, sleepiness. Loss of an ability to learn new things and doing things by rote. Oral Cavity problems such as Inflammation of the mouth, loss of bone around teeth, ulcerated gums and other areas in the mouth, loose teeth, darkening of gums, taste of metal and bleeding of gums. Digestive tract problems such as cramps, inflamed colon, GI problems, diarrhoea and other digestive problems. Cardiovascular problems such as weak pulse, blood pressure changes and chest pain, or feeling of pressure in the chest area. Respiratory problems such as weakness and problems with breathing, emphysema and eoughing persistently. Neurological problems such as headaches, vertigo, tinnitus, shaking in various areas of the body (eye lids, feet etc) [14,16]. Symptoms in children, mercury poisoning in Children is a cause of many symptoms of developmental disorders including Autism, decreased eye contact, flat affect, repeating certain actions over and over again, not responding to their name, not looking at an object that is being pointed at by another, poor concentration or attention, sensitivity to sensory stimulation [10,22, 23].

RECOMMENDED SAFETY INTAKE

The recent recommendation by the Environmental Protection Agency (EPA) that the allowable or safe daily intake of methyl mercury be reduced from 0.5 µg of mercury per kilogram of body weight per day, the threshold established by the World Health Organization in 1978, to 0.1 µg of mercury per kilogram per day, EPA [15]. The Food and Drug Administration (FDA) has recommended that pregnant women, breastfeeding mothers, and young children avoid eating fish with a high mercury content (>1 ppm), such as shark, swordfish, tilefish, and king mackerel. This also includes fresh and frozen tuna (mercury content between 0.5 ppm and 1.5 ppm) but not canned tuna, which consists of smaller, shorter-lived species with lower mercury levels. From a nonprofessional perspective, this translates into a weekly consumption of one can (198 g or 7 oz) of tuna for an adult.7 Rather than ban the sale of these species, Health Canada recommends that they be consumed no more than once per week or once per month by children and by women of childbearing age.8 Mercury levels in freshwater fish vary, but, in general, bass, pike, muskellunge, and walleye have high levels of mercury and should be eaten in moderation. Provincial guidelines for sport fish often mirror federal seafood recommendations, Ye X [22].

CONCLUSIONS AND SUGGESTIONS

Elemental (metallic) mercury and its compounds are toxic and exposure to excessive levels can permanently damage or fatally injure the brain and kidneys. Elemental mercury can also be absorbed through the skin and cause allergic reactions. Ingestion of inorganic mercury compounds can cause severe renal and gastrointestinal toxicity. Organic compounds of mercury

such as methyl mercury are considered the most toxic forms of the element. Exposures to very small amounts of these compounds can result in devastating neurological damage and death. For fetuses, infants and children, the primary health effects of mercury are on neurological development. Even low levels of mercury exposure such as result from mother's consumption methyl mercury in dietary sources can adversely affect the brain and nervous system. Its prolonged period of latency, ambiguous symptoms and the activation of generalised toxic mechanisms call for urgent efforts to be made in basic research to help determine as clearly as possible the way this metal acts in the body. This knowledge will provide us not only with the way to obtain therapies but also with the hope of developing biomarkers that make it possible to carry out early and reliable diagnoses of the damage done and of individual susceptibility.

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