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Luteinizing hormone provides a causal mechanism for mercury associated disease

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SUMMARY

Previous studies have demonstrated that the pituitary is a main target for inorganic mercury (I-Hg) deposition and accumulation within the brain. My recent study of the US population (1999–2006) has uncovered a significant, inverse relationship between chronic mercury exposure and levels of luteinizing hormone (LH). This association with LH signifies more than its presumed role as bioindicator for pituitary neurosecretion and function. LH is the only hormone with a rare and well characterized, high affinity binding site for mercury. On its catalytic beta subunit, LH has the structure to preferentially bind inorganic mercury almost irreversibly, and, by that manner, accumulate the neurotoxic element. Thus, it is likely that LH is an early and significant target of chronic mercury exposure. Moreover, due to the role of LH in immune-modulation and neurogenesis, I present LH as a central candidate to elucidate a causal mechanism for chronic mercury exposure and associated disease.

Hypothesis

The biological association between chronic mercury exposure and luteinizing hormone represents a central, causal mechanism for mercury associated disease.

Chronic mercury exposure and deposition

Mercury is a potent neurotoxin that directly impairs many areas and functions of the neuron including calcium channels [1–3], protein synthesis [4], mitochondria [4], and neurite outgrowth [5]. Both the aforementioned neurotoxicity and a human disease response to mercury exposure has been shown to be dependent on reaching a critical threshold concentration [6]. Therefore, in cases of acute mercury poisoning, the direct neurotoxic effect of mercury in the brain may surpass this threshold and elicit a disease response. However, in cases of chronic mercury exposure, mercury concentrations in the brain may remain beneath the critical threshold concentration and therefore a direct relationship between chronic mercury exposure and neurotoxicity is not evident, prima facie.

In toxicological studies of chronic mercury exposure in primates, organic mercury has been shown to demethylate and form inorganic mercury deposits which persist in the brain for years [7,8]. In both primates and humans, inorganic mercury deposits preferentially target the pituitary where they accumulate [8,9].

The accumulation of inorganic mercury deposits in the body is reasoned to be detectable by changes of inorganic mercury levels in the blood [10]. In a recent human population dependent on fish, inorganic mercury accumulation in the blood has been shown to be associated with chronic mercury exposure [11]. In another recent study, I used inorganic mercury exposure as the bioindicator of chronic mercury exposure within the US population [12] and discovered a significant, inverse relationship between chronic mercury exposure and luteinizing hormone (LH).

High affinity target

As the pituitary had previously been shown to be a principle site in the brain for inorganic mercury deposition and accumulation, I had used LH as a general bioindicator for pituitary neurosecretion and function. Upon an extensive literature review of LH, I unearthed a significant and clear explanation for why LH is associated with chronic mercury exposure. Based on its unique amino acid sequence, thioredoxin is a high affinity target for inorganic mercury [13]. Due to a specific sequence of cysteine residues, free sulfur bonds will bind almost irreversibly to inorganic mercury, thioredoxin will tend to bio-accumulate mercury, and this interaction has been hypothesized to be a molecular mechanism for mercury toxicity. In 1990, evidence was presented that LH was the only hormone to share that specific amino acid sequence found in thioredoxin [14]. Furthermore, this specific sequence was found on the catalytic, beta subunit of LH. Therefore, it is logical to assume that

Abbreviations: LH, luteinizing hormone; I-Hg, inorganic mercury; CH_3Hg, methyl mercury; NHANES, national health and nutrition examination survey; AD, Alzheimer's disease; HPA, hypothalamic–pituitary–adrenal axis.

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LH, like thioredoxin, is a high affinity target for inorganic mercury. As such, LH will preferentially and almost irreversibly bind to inorganic mercury. This specific, high affinity binding should result in the toxico-kinetic properties of mercury bio-accumulation. As LH is secreted by the pituitary, a main site for inorganic mercury deposition and accumulation, and as it seems to be a high affinity target for inorganic mercury, it is reasonable to assume that the recently reported relationship with chronic mercury exposure represents a significant, biological association. Furthermore, understanding the unique role of LH in the body, an association with chronic mercury exposure presents LH as a strong candidate to elucidate a causal mechanism for mercury neurotoxicity and associated disease.

The role of LH

LH is not only a high affinity target for mercury, located in the prime area of mercury deposition and accumulation, but it also regulates diverse systems whose impairment is symptomatic of mercury associated disease. LH is secreted by the anterior pituitary and mediates androgen stimulation, mitogenesis, and immune regulation [15–18].

Specific neuronal tracts have been shown to produce luteinizing hormone releasing hormone (LHRH) within the adult brain to modulate glial formation and the complex neuronal-macroglia networks that are crucial to brain development, plasticity, function, and the neuroimmune inflammatory response [17]. LHRH is also found on human peripheral lymphocytes, indicating a role for LH in mediating both the central and peripheral immune systems [19]. As a mitogen, LH is not only involved as a gonadotroph, but also in the birth of neurons. Recently, LH was demonstrated in both mice [20] and sheep [21] to directly induce neurogenesis in the adult hippocampus, the area of the brain associated with learning and memory.

LH is directly involved in regulating all of the systems that are symptomatic of mercury associated disease; impaired immune response, inflammation, disruption of glia-neuronal networks, and impaired neurogenesis. Therefore, it is reasonable to assume that the biological association between chronic mercury exposure and luteinizing hormone represents a causal mechanism to delineate the pathology from chronic mercury exposure and deposition, to an impaired endocrine system and the defining characteristics of mercury associated disease.

Mercury, LH, and associated disease

Certainly there are strong and persistent associations between mercury exposure and both neurodevelopmental [22–31] and neurodegenerative [32–35] disease. Moreover, there are strong and consistent associations, in multiple animal models, and within the human population, that the endocrine system is a main target of mercury neurotoxicity and effect [36]. As LH is the only hormone with the known high affinity binding site for mercury, as it is located in the pituitary, a demonstrated sink for mercury deposition and accumulation, and as LH has a biological association with chronic mercury exposure, it is logical to propose that LH represents a main candidate to elucidate a disease response to mercury exposure.

The hypothalamic–pituitary–adrenal axis (HPA) is programmed during neonatal development, and early exposure to toxins can disrupt the delicate endocrine system to program an imbalanced immune system that is predisposed towards an inflammatory response [16]. Experts agree that any disturbance of the HPA system leads to an increased risk of infection, inflammation, and autoimmune disease [37,38]. Inflammatory response and an impaired immune system are characteristic of mercury neurotoxicity [39–42] and both neurodevelopmental [43,44] and neurodegenerative [45] diseases that are associated with mercury exposure. LH plays a key role in neuroprotection and inflammatory response within the central nervous system [46].

The endocrine system has been implicated for a central role in the pathogenesis of autism [47–49]. LH is a gonadotroph and is primarily known for its role in the induction of androgens. Strikingly, Autism is characterized by an imbalance in androgen levels [50,51]. While some medical professionals have hypothesized a direct interaction between mercury exposure and androgen receptors [52], this perspective postulates that the effect of mercury is primarily upstream of those receptors, and, an alternative hypothesis is presented, that focal targeting of LH by mercury exposure and deposition in the pituitary is responsible for the apparent aberrant androgen levels in mercury associated neurodevelopmental disease such as autism.

Mounting evidence indicates that inflammation impairs neurogenesis, the required migration of neuronal precursors, and the proper incorporation of new neurons into the cytoarchitecture [53–55]. The pituitary secretes hormones which regulate thyroid hormones. Mercury exposure has been demonstrated to impair thyroid hormone function [56,57]. Impaired thyroid hormone function has been linked to impaired migration of neuronal precursors and disruption of the delicate incorporation of neurons into the developing cytoarchitecture [58]. Inorganic mercury deposits are associated with neurotoxic and immune pathways associated with neurodegeneration and LH provides a compelling candidate to explain a causal relationship [59].

As mentioned previously, mercury exposure has been associated with age related neurodegenerative disease [32–35]. "Endocrine abnormalities of the hypothalamic–pituitary–adrenal (HPA) system in patients with Alzheimer's and Parkinson's disease have been described repeatedly," Hartmann [60]. Alzheimer's disease (AD) pathology is marked by elevated serum and neuronal levels of LH [46]. Brain regions most affected by AD pathology show elevated expression of LH [15], and moreover, in cell culture, LH accelerates the formation of amyloid plaques, a defining pathological characteristic of AD.

Trends of chronic mercury exposure

From analysis of data on the human population from 1999 to 2000, it was estimated that 300,000–500,000 children may be born during those years with elevated risks of neurodevelopmental disease based on their exposure to mercury [61]. However, these risks of disease response to mercury exposure may be rising over time due to rising levels of chronic mercury exposure [12]. In fact, atmospheric mercury deposition is rising over time [62], mercury levels are rising in the oceans [63], and global mercury emissions are projected to continue rising in the future [64]. Therefore, while a causal mechanism between chronic mercury exposure and associated disease is not clearly understood, this time trend of rising exposure levels makes it a public health and medical imperative to investigate the mechanisms underlying mercury associated disease in order to prevent, diagnose, and treat this serious, emergent health threat.

Conclusion

Certainly it is well understood, in multiple human and animal models, that mercury exposure targets the endocrine system [36]. However, the relationship between endocrine impairment and mercury associated disease is poorly understood. This perspective posits that luteinizing hormone represents a promising, and viable candidate to provide a causal mechanism for mercury asso-