Further Thoughts on Mercury, Epigenetics, Genetics and Amyotrophic Lateral Sclerosis

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I read with interest the recent paper by Callaghan et al. [1] reviewing the role of exposure to the metals lead, mercury and selenium and potential epigenetic factors in the development of amyotrophic lateral sclerosis (ALS). Callaghan et al. [1] have considered whether heavy metal interaction with epigenetic phenomena that govern DNA modifications such as DNA-bound histones, DNA methylation and chromatin remodeling may be responsible for some of the toxic actions of heavy metals which in turn may play a role in the etiology of ALS. Several aspects of their discussion regarding mercury in particular caught my attention.

With regard to mercury interfering with epigenetic mechanisms, it has been observed previously that cysteine-S-methylmercury conjugates are structurally similar to methionine, and are suspected to function as molecular mimics of methionine at certain amino acid transporters [2]. This being the case, and given that methionine plays a role in providing methyl groups to DNA methyltransferase, it is worth considering: might molecular mimicry of methionine allow organic mercury conjugates to interfere with DNA methylation thereby exerting epigenetic toxic effects?

Moving away from epigenetic considerations, Callaghan et al. [1] discuss the use of chelators to estimate

mercury body burden. They correctly point out that chelation-provoked urinary mercury levels may not reflect the amount of mercury to which motor neurons (or the brain) are exposed. However, it must also be considered that such ‘chelation challenge’ testing is subject to potential interactions from a variety of nutritional factors, such as blood thiol levels, zinc levels, selenium levels and other factors as discussed previously [3]. Each such factor represents a potential confounding variable that may go some way towards explaining the conflicting results found wherever chelation challenge tests are used in practice. An additional concern regarding chelation challenge testing revolves around the large bolus doses that are often used and may carry inherent risks, both from the side-effects of the chelators themselves and the potential to redistribute body burdens of mercury [3].

A further consideration is that while it is possible that mercury exerts toxicological effects through epigenetic mechanisms, we must not overlook recent discoveries of conventional genetic polymorphisms that have been associated with atypical neurobehavioural responses on exposure to mercury. Polymorphisms of CPOX, BDNF, 5-HTTLPR and COMT have all been associated with atypical neurobehavioural responses on exposure to mercury in combination with carriage of the relative gene

[4–7]. Using neurobehavioural testing, low-level mercury exposure was seen to be independently significantly associated with deficits in manual coordination skills [4]. Furthermore, the combined carriage of CPOX4 and exposure to chronic low levels of mercury was found to be significantly associated with a deficit in the ‘symbol-digit_{rate} test’ – a combined test of visual processing and motor reaction time [4]. Combined chronic low-level mercury exposure and carriage of a BDNF polymorphism has been significantly associated with deficits in manual coordination skills [5]. Of particular note amongst the above polymorphisms, CPOX4 has been associated with the occurrence of an atypical urinary porphyrin that occurs (in adults) on exposure to mercury – potentially acting as both a marker for mercury exposure and CPOX4 polymorphism [8]. These characteristics have led to the use of urinary porphyrins to investigate

mercury exposure in autistic children [9]. It should be noted that the above associations were found using neurobehavioural testing designed to investigate the cognitive functions involved in motor function. However, this does not exclude toxicity directly affecting motor function. Furthermore, these associations have been found at low blood mercury concentrations – in fact, levels were comparable to the ‘background’ blood mercury concentration of the general population.

I am not aware of any studies to date that have investigated for associations between carriage of the aforementioned polymorphisms, concurrent mercury exposure, levels of atypical urinary porphyrins and the occurrence of ALS. Given the conflicting evidence regarding a role of mercury in the etiology of ALS as outlined by Callaghan et al. [1], this could prove to be an illuminating area of future research.

References

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