bonds with any oxidized form of Hg. Selenium (Se) has a lower natural geochemical abundance than any other known nutrient element. However, biologically important selenols include GSH peroxidase and thioredoxin reductase, which are discussed later.

Mercury also targets disulfide bonds, which provide much of the tertiary and quaternary structure for proteins. For example, the cys-loop family of ion channels employs a disulfide bond as the active site of its extracellular domain. By breaking this disulfide bond, Hg alters the structure and function of the ion channel, which thus alters mineral transport into the cell, resulting in mineral dyshomeostasis, disruption in the cell's ability to maintain proper ionic metal equilibrium (homeostasis) in response to changing environmental conditions.

These molecular mechanisms lead to the toxic effects described below, including increased oxidative stress, depletion of antioxidant defenses, alteration of essential mineral homeostasis, mitochondrial dysfunction, immune effects including alteration of gut flora, and dysregulation of hormones and neurotransmitters. These effects in turn are likely to cause issues of fatigue, inflammation, immunity, and mood.

4.1. Pro-oxidant effects

In the central nervous system, Hg species increase extracellular glutamate, an excitatory neurotransmitter, both by inhibiting glutamate uptake and by stimulating glutamate release into the synaptic cleft (Farina *et al.* 2013). Overactivation of the NMDA glutamate receptor leads to an increased influx of calcium ions (Ca^{2+}) due to the receptor's high permeability to this mineral. High intracellular calcium activates a number of enzymes that are associated with the generation of reactive species of oxygen and nitrogen, resulting in oxidative stress, altered membrane potentials, and mitochondrial dysfunction (Farina *et al.* 2013). Furthermore, overactivation of the NMDA glutamate receptor is associated with depression (Sowa-Kućma *et al.* 2013; Zarate *et al.* 2013) and suicide (Sowa-Kućma *et al.* 2013).

4.2. Effects on antioxidant defense

Glutathione is a key antioxidant and coenzyme in biological systems. The glutathione system includes reduced (GSH) and oxidized (GSSG) forms of glutathione; the enzymes required for its synthesis and recycling; and the enzymes required for its use in metabolism and in mechanisms of defense against free radical-induced oxidative damage. The glutathione molecule itself, as well as the active sites for several enzymes in the glutathione system, contain thiols (as cysteine) which are targets for Hg binding. By binding thiols in glutathione and its related enzymes, Hg species deplete the available level of this important molecule and also impair its synthesis, use, and recycling. The many functions of glutathione include detoxification, metabolic regulation, maintenance of neurotransmitters, protection of membranes, and modulation of signal transduction (Limón-Pacheco and Gonsebatt 2010). A common pathological hallmark in various diseases is the increase in oxidative stress and the failure of antioxidant systems, marked by a decrease in GSH (Limón-Pacheco & Gonsebatt 2010).

Thioredoxins are a class of antioxidant proteins that exert a range of regulatory activities by chemically reducing target molecules. Like the glutathione system, the thioredoxin system comprises the molecule itself and the enzymes required for its synthesis, use, and recycling. Thioredoxins contain two thiol active sites, which are targets for Hg. The enzyme that recycles thioredoxin, thioredoxin reductase, contains both a selenocysteine and a disulfide active site, which are targets for Hg (Branco *et al.* 2012a,b). Thus, Hg depletes thioredoxin and also impairs its recycling. The result is a shift in the cellular redox balance, toward oxidation, thus altering regulatory activities.

4.3. Effects on zinc and copper status / homeostasis

Metallothioneins are a class of cysteine-rich proteins whose function is not entirely clear but which appear to bind, store, and regulate metals including Cu and zinc (Zn). Mercury and similar metals induce apometallothionein, which bind/s Hg itself, thus protecting against toxicity, while displacing Cu and Zn species, disturbing their homeostasis (Bjørklund 2013; Clarkson 1987; Davis & Mertz 1987; Hambidge *et al.* 1986; Kostial 1986; Underwood 1977). This disturbance in the metabolism and storage of Cu and Zn may be an important contributory cause of Zn deficiency. At least 300 Zn-dependent enzymes are known to exist, and there are even more Zn-dependent transcription factors (Oteiza & Mackenzie 2005; Prasad 2012). Zinc deficiency may not only cause immunosuppression (Hambidge *et al.* 1986; Prasad 1995, 1997), which may play a role in CFS, but may also have harmful consequences for the brain.

Evidence suggests that Cu and/or Zn levels are abnormal in CFS, FM, depression, anxiety, and suicide. CFS and FM patients show a deficiency in serum Zn (Maes *et al.* 2006; Werbach 2000), and these disorders show improvement in clinical symptoms with Zn supplementation (Maes *et al.* 2008). Studies in both depression and anxiety show low serum Zn levels and high serum Cu levels (Chang *et al.* 2013; Islam *et al.* 2013; Narang *et al.* 1991; Tao *et al.* 2013; Sowa-Kućma *et al.* 2013; Swardfager *et al.* 2013a,b). In addition, low Zn and high Cu levels are associated with high symptom severity in depression (Russo 2011). Further, low Zn levels are found in patients who have attempted suicide (Gronek & Kolomaznik 1989). Table 2 provides examples of Hg's effects and the underlying mechanisms that might explain many symptoms in CFS, FM, depression, anxiety, and suicide.

4.5. Gut microbe effects

Normal gut flora is a modulator of behavior (Diaz Heijtz *et al.* 2011) and immunity (Hansen *et al.* 2012;