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# Mechanisms involved in the transport of mercuric ions in target tissues

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## Abstract

Mercury exists in the environment in various forms, all of which pose a risk to human health. Despite guidelines regulating the industrial release of mercury into the environment, humans continue to be exposed regularly to various forms of this metal via inhalation or ingestion. Following exposure, mercuric ions are taken up by and accumulate in numerous organs, including brain, intestine, kidney, liver, and placenta. In order to understand the toxicological effects of exposure to mercury, a thorough understanding of the mechanisms that facilitate entry of mercuric ions into target cells must first be obtained. A number of mechanisms for the transport of mercuric ions into target cells and organs have been proposed in recent years. However, the ability of these mechanisms to transport mercuric ions and the regulatory features of these carriers have not been characterized completely. The purpose of this review is to summarize the current findings related to the mechanisms that may be involved in the transport of inorganic and organic forms of mercury in target tissues and organs. This review will describe mechanisms known to be involved in the transport of mercury and will also propose additional mechanisms that may potentially be involved in the transport of mercuric ions into target cells.

### Keywords

Inorganic mercury; Methylmercury; Transport; Kidney; Brain

## Introduction

Since the beginning of the industrial revolution, the global human population has been faced with the problem of environmental pollution. As the human population has grown, the level of environmental pollution has increased, making it a serious, world-wide health problem (SOER 2015). Humans are exposed regularly to environmental pollutants in air, soil, water, and/or food. While air pollution represents a major route of human exposure to toxicants [because exposure to this form of pollution is nearly unavoidable (WHO 2016)], oral exposure via ingestion of contaminated water and/or food also represents an important route of human exposure to toxicants. As one would expect, exposure to toxicants via multiple routes enhances one's total toxicant burden, which can negatively affect health outcomes in certain populations.

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Mercury (Hg) is a ubiquitous metal pollutant that can be found in air, soil, and water. It exists in metallic, inorganic, and/or organic forms in the environment, and its presence in the world-wide environment is becoming increasingly problematic. While a fraction of Hg enters the environment through natural processes such as volcanic activity and the breakdown of minerals in rocks and soils, the majority of Hg is released into the environment through industrial processes such as mining and the burning of fossil fuels (ATSDR 1999). It has been estimated that the combustion of fossil fuels (primarily coal), biofuels, and wastes accounts for the greatest portion (approximately 35–77 %) of anthropogenic Hg emissions (Ambrose et al. 2015). Approximately half of these emissions can be attributed to coal-fired power plants (Ambrose et al. 2015; Holzman 2010), which represent the largest source of environmental Hg in the USA (USEPA 1997, 1998). Although the regulations regarding Hg emissions have become more stringent in recent years, the regulatory mandates are in need of improvement (Rallo et al. 2012). Elemental Hg released from power plants can remain in the atmosphere for up to 2 years and can be transported to a different hemisphere before settling in soil and water (Holzman 2010). It is important to note that China is the largest emitter of Hg in the world (Liang et al. 2015) and this Hg can easily spread to multiple continents. Given the ability of Hg to travel in the atmosphere and the lack of strict regulatory guidelines in many countries, the deposition of Hg in the environment continues to be a major problem.

Although exposure to Hg through environmental sources may affect a large percentage of the population, this route of exposure does not often lead to toxicological consequences in humans. In contrast, human exposure via dental amalgams, medicinal therapies, and/or dietary sources has been shown to lead to toxicological consequences (ATSDR 1999; Clarkson and Magos 2006; Risher and De Rosa 2007; Zalups 2000). Of the different routes of exposure, humans are exposed to the greatest levels of Hg via ingestion of food contaminated with organic forms of Hg (i.e., methylmercury; $CH_3Hg^+$). High levels of $CH_3Hg^+$ are found often in the muscle of large predatory freshwater and saltwater fish, such as northern pike, salmon, swordfish, tuna, and shark. Accumulation of Hg in tissues of these fish is related primarily to their ingestion of other contaminated fish, their longevity in contaminated waters, and their inability to efficiently eliminate Hg (Ward et al. 2010). Following the ingestion of contaminated food, $CH_3Hg^+$ is absorbed readily by the gastrointestinal tract and subsequently enters systemic circulation, which facilitates the delivery of mercuric ions to target organs (ATSDR 1999).

Occupational exposure also represents a major route of exposure to Hg. In particular, artisanal and small-scale gold mining (ASGM) are major sources of occupational exposure to Hg. Even though these activities have been banned in many countries, millions of people continue to use these methods to extract gold from ore. Indeed, recent estimates suggest that over 16 million artisanal miners remain active, particularly in South America (Seccatore et al. 2014). The air around amalgam burning sites often has very high levels of mercury vapor and usually exceeds the World Health Organization (WHO) limits for exposure (Gibb and O'Leary 2014; Nakazawa et al. 2016). Furthermore, the concentration of Hg in the urine of adults often exceeds the recommended limits, suggesting that exposure to Hg via mining activities increases the probability of developing acute and/or chronic pathologies (Kristensen et al. 2014). Children are also at risk of exposure to toxic levels of Hg due to

participation in amalgam burning or by being in the proximity of the amalgam burning sites. Some of these children have been shown to exhibit long-term neurological deficits (Ohlander et al. 2016), suggesting that they have been exposed to toxic levels of Hg.

Exposure to the various forms of Hg can lead to detrimental effects in many organ systems. These include, but are not limited to, the cardiovascular (Carmignani et al. 1992; Soni et al. 1992; Wakita 1987; Wang et al. 2000; Warkany and Hubbard 1953), gastrointestinal (Afonso and De Alvarez 1960; Bluhm et al. 1992; Lundgren and Swensson 1949; Murphy et al. 1979), neurological (Jaffe et al. 1983; Lin and Lim 1993), hepatobiliary (Jaffe et al. 1983; Murphy et al. 1979; Samuels et al. 1982), and renal (Murphy et al. 1979; Rowens et al. 1991; Samuels et al. 1982) systems.

When evaluating the handling of mercuric ions in biological systems, one must consider the chemical characteristics of mercuric ions. Mercuric ions have a high affinity for nucleophilic functional groups, particularly sulfhydryl (thiol; -*S*) groups. Given the tendency of mercuric ions to form strong bonds with thiols, one can assume that all mercuric ions within biological systems are bound to thiol-containing molecules, such as glutathione (GSH), cysteine (Cys), homocysteine (Hcy), *N*-acetylcysteine (NAC), and albumin. Mercuric ions do not likely exist as inorganic salts, or in an unbound, “free” ionic state (Hughes 1957).

Inorganic mercury ($Hg^{2+}$) forms linear II, coordinate covalent complexes with low molecular weight thiol-containing molecules (Fuhr and Rabenstein 1973; Rubino et al. 2004), while organic forms of mercury, such as methylmercury ($CH_3Hg^+$), bind to thiol-containing molecules to form linear I, coordinate covalent complexes (Fig. 1). Mercuric conjugates of thiol-containing molecules appear to be thermodynamically stable in an aqueous environment throughout a pH range of 1–14 (Fuhr and Rabenstein 1973). The affinity constant for mercuric ions bound to thiolate anions is approximately $10^{15}$–$10^{20}$. Although the bond between a mercuric ion and a thiol-containing molecule appears to be stable in simple aqueous solutions, it is likely that this interaction is much more complex within living organisms (Fuhr and Rabenstein 1973). Various factors such as thiol competition and exchange may lead to an unstable bond between mercuric ions and certain thiol-containing molecules. For example, shortly after exposure to $Hg^{2+}$, most of the mercuric ions present in plasma are likely bound to thiol-containing proteins such as albumin (Cember et al. 1968; Friedman 1957; Lau and Sarkar 1979; Mussini 1958). Interestingly, the amount of Hg in blood is reduced rapidly following exposure to Hg, suggesting that mercuric ions are being taken up by target cells. Yet, Hg–albumin complexes do not appear to be taken up readily by target cells such as proximal tubular cells (Zalups and Barfuss 1993). Therefore, it appears that Hg bound to plasma proteins (e.g., Hg–albumin) dissociate in the presence of other thiols, permitting the mercuric ions to bind to the most abundant non-protein thiol, which may form a transportable mercuric complex that can be taken up more readily into target cells.

## Transport of inorganic mercury

### Intestinal transport of inorganic mercury

Understanding the mechanisms responsible for the intestinal transport of inorganic mercury ($Hg^{2+}$) is important considering that exposure to this metal may occur via consumption of food and/or liquids contaminated with $Hg^{2+}$. It has been suggested that the transport of $Hg^{2+}$ across the plasma membranes of enterocytes utilizes both passive and active mechanisms (Andres et al. 2002; Hoyle and Handy 2005; Laporte et al. 2002). In addition, the method by which $Hg^{2+}$ is transported across intestinal enterocytes is thought to be dependent upon the species of $Hg^{2+}$ presented to enterocytes (Foulkes 2000). It is important to note that the species of $Hg^{2+}$ present in the lumen of the intestine is highly dependent upon the components of ingested food in that ingested food often has a high concentration of thiol-containing molecules, such as amino acids and peptides, which can bind to $Hg^{2+}$. Thiol *S*-conjugates of $Hg^{2+}$ formed in the lumen of the gastrointestinal tract may be similar in shape and size to certain endogenous molecules (e.g., amino acids and/or polypeptides) that are absorbed along the small intestine. Owing to these similarities and because amino acid and peptide transporters are prevalent in enterocytes (Dave et al. 2004; Ganapathy et al. 2001), it is possible that thiol *S*-conjugates of $Hg^{2+}$ are taken up into enterocytes by one or more of amino acid and/or peptide transporters. The duodenum, which is a major site of amino acid absorption, also appears to be the initial site of $Hg^{2+}$ absorption (Endo et al. 1984). This observation supports the theory that amino acid and/or peptide transporters may be involved in the intestinal uptake of mercuric species. The identities of specific amino acid/peptide transporters that are involved in the intestinal uptake of $Hg^{2+}$ have not yet been reported.

A fraction of ingested $Hg^{2+}$ may be taken up following ligand exchange whereby the mercuric ion dissociates from the thiol to which it is bound and is transported subsequently into cells via one or more ion transporters. The divalent metal transporter 1 (DMT1; *SLC11A2*), which is localized in the apical membrane of enterocytes (Canonne-Hergaux et al. 1999), may play a role in the uptake of mercuric ions. In vivo studies in mice showed that decreased expression of intestinal DMT1 corresponded to a decrease in the intestinal accumulation of $Hg^{2+}$. These data suggest that DMT1 may play a role in the intestinal uptake of $Hg^{2+}$ (Ilback et al. 2008). Recently, more direct studies in yeast and cultured enterocytes (Caco-2 cells) indicate that DMT1 is capable of mediating the cellular uptake of mercuric ions (Vazquez et al. 2015).

The intestine also appears to play an important role in the net fecal elimination of $Hg^{2+}$. Mercuric ions in blood may cross enterocytes and enter the intestinal lumen by paracellular and/or transcellular mechanisms (Hoyle and Handy 2005; Sugawara et al. 1998; Zalups et al. 1999). Data from in vivo studies in rats with ligated bile ducts indicate that a fraction of the $Hg^{2+}$ that is excreted in the feces is due to secretion of $Hg^{2+}$ from blood into the intestinal lumen (Zalups 1998). This secretion likely involves the transport of thiol *S*-conjugates of $Hg^{2+}$, which may occur via amino acid transporters, multidrug resistance-associated proteins (MRPs), and organic anion transporters (OATs). Many amino acid transporters are counter-exchangers, and thus, they may be able to mediate the export of mercuric complexes in exchange for amino acids at the luminal and basolateral membranes. MRPs have been

characterized as export proteins, and thus, they may be involved in the export of $Hg^{2+}$ across the basolateral and luminal membrane of enterocytes. At the basolateral membrane, MRP3 (*ABCC3*) mediates the uptake of compounds from the interstitial space into enterocytes and, therefore, this carrier may also be involved in the basolateral uptake of $Hg^{2+}$ into enterocytes (Prime-Chapman et al. 2004; Rost et al. 2002; Shoji et al. 2004; Yokooji et al. 2007). MRP4 is also localized in the basolateral membrane of enterocytes (Ming and Thakker 2010); however, in vitro studies have suggested that mercuric species are not substrates of MRP4 (Bridges et al. 2013). The export of mercuric species from within enterocytes, across the apical membrane, and into the intestinal lumen may be mediated by MRP2 (*ABCC2*). MRP2 has been shown to be involved in the intestinal secretion of organic anions (Itagaki et al. 2008) and has been implicated previously in the transport of mercuric ions (Bridges et al. 2008a, b, 2011). Owing to the broad substrate specificity of MRP2 and MRP3, it is possible that they may be involved in the basolateral to apical movement of thiol *S*-conjugates of $Hg^{2+}$ across enterocytes. Other members of the MRP family, including MRP5 (*ABCC5*), MRP6 (*ABCC6*), and MRP7 (*ABCC7*), have been identified in enterocytes (Maher et al. 2005); however, the membrane localization of these proteins and their ability to transport mercuric species are unknown currently. OATs have been implicated in the transport of mercuric species in other organs and target cells; therefore, it is possible that one or more OATs may be involved in the intestinal secretion of certain mercuric species. OAT2 (*SLC22A7*) and OAT10 (*SLC22A13*) have been identified in the intestine although the ability of either carrier to mediate the transport of mercuric species is unknown at present.

## Renal transport of inorganic mercury

Following exposure to elemental or inorganic forms of Hg, the majority of mercuric ions accumulate in the kidneys (Ashe et al. 1953; Clarkson and Magos 1966; Friberg 1959; Friberg et al. 1957; Hahn et al. 1990). In fact, the uptake and accumulation of $Hg^{2+}$ in the kidneys occurs rapidly with as much as 40 % of a non-nephrotoxic dose (0.5 μmol $kg^{-1}$) of $Hg^{2+}$ present in the kidneys of rats within 1–3 h after exposure (Zalups 1993a). $Hg^{2+}$ accumulates primarily in the segments of the nephron that are located in the cortex and outer stripe of the outer medulla (Berlin and Gibson 1963; Berlin and Ullberg 1963; Taugner 1966; Taugner et al. 1966). Histochemical and autoradiographic studies using mice and rats indicate that the accumulation of $Hg^{2+}$ in the renal cortex and outer stripe of the outer medulla occurs almost exclusively along the *pars convoluta* and the *pars recta* of the proximal tubule (Hultman et al. 1985, 1992; Hultman and Enestrom 1986, 1992; Magos et al. 1985; Rodier et al. 1988; Taugner et al. 1966; Zalups 1991). Although the proximal tubule is the primary site of accumulation for mercuric ions, the possibility remains that other renal tubular segments may also take up, accumulate, and export mercuric ions.

The proximal tubular uptake of $Hg^{2+}$ has been shown to utilize mechanisms localized in the luminal and basolateral plasma membranes of proximal tubular cells (Zalups and Minor 1995). At the luminal membrane, a Cys *S*-conjugate of $Hg^{2+}$ (Cys-*S*-Hg-*S*-Cys) appears to be the primary species of $Hg^{2+}$ transported into cells. It appears that this conjugate is formed from GSH *S*-conjugates of $Hg^{2+}$ (G-*S*-Hg-*S*-G), which are filtered freely at the glomerulus and may also be secreted from proximal tubular cells themselves. Once G-*S*-Hg-*S*-G enters the tubular lumen, it is thought to be degraded rapidly and sequentially by γ-

glutamyltransferase and cysteinylglycinase to yield either Cys-*S*-Hg-*S*-Cys or a mixed *S*-conjugate of $Hg^{2+}$ (Berndt et al. 1985; de Ceaurriz et al. 1994; Tanaka-Kagawa et al. 1993; Tanaka et al. 1990; Zalups 1995). In vitro studies in which isolated proximal tubules were perfused with various conjugates of $Hg^{2+}$ also indicate that Cys-*S*-Hg-*S*-Cys is readily taken up at the luminal membrane of proximal tubular cells (Cannon et al. 2000, 2001).

Subsequent experiments in isolated, perfused proximal tubules showed that the luminal uptake of Cys-*S*-Hg-*S*-Cys involves at least one $Na^+$-dependent and one $Na^+$-independent amino acid carrier (Cannon et al. 2001). Given the similarities in size and shape between Cys-*S*-Hg-*S*-Cys and the amino acid cystine (Fig. 1), it was proposed that the luminal uptake of Cys-*S*-Hg-*S*-Cys into proximal tubular cells may involve one or more cystine transporters. Indeed, recent in vitro studies have shown that System $b^{0,+}$ is involved in the $Na^+$-independent transport of Cys-*S*-Hg-*S*-Cys into proximal tubular cells (Bridges et al. 2004). System $b^{0,+}$ is a heterodimeric transporter, comprised of $b^{0,+}$AT (*SLC7A9*) and rBAT (*SLC3A1*), that mediates the luminal uptake of cystine and neutral and basic amino acids into proximal tubular cells (Palacin et al. 1998, 2001). While additional studies have shown that Hcy *S*-conjugates of $Hg^{2+}$ (Hcy-*S*-Hg-*S*-Hcy) are also transported by System $b^{0,+}$ (Bridges and Zalups 2004), it appears that that mercuric conjugates of GSH (G-*S*-Hg-*S*-G), *N*-acetylcysteine (NAC-*S*-Hg-*S*-NAC), and cysteinylglycine (CysGly; CysGly-*S*-Hg-*S*-CysGly) are not substrates of this carrier (Bridges et al. 2004). Together, these data indicate that Cys-*S*-Hg-*S*-Cys and Hcy-*S*-Hg- *S*-Hcy gain access to proximal tubular cells at the luminal plasma membrane via System $b^{0,+}$ (Fig. 2).

Recently, a novel aspartate/glutamate transporter (AGT1; *SLC7A13*) has been identified in the luminal membrane of the epithelial cells lining the S3 segments of proximal tubules (Nagamori et al. 2016). This transporter has been shown to mediate the luminal uptake of cystine and it appears to co-localize with rBAT. The ability of AGT1 to transport mercuric species has not been shown, but we propose that this carrier may be involved in some aspect of the uptake of mercuric ions along the S3 segment of proximal tubules.

Another transporter that may be involved in the luminal uptake of mercuric species is OAT5 (*SLC22A10*). This carrier is localized in the apical plasma membrane of proximal tubular cells and has been shown to mediate the cellular uptake of a variety of organic anions from the tubular lumen (Anzai et al. 2005). To date, there are no data implicating OAT5 in the luminal uptake of mercuric species.

The basolateral uptake of $Hg^{2+}$, whereby mercuric species are taken up from peritubular blood into proximal tubular cells, represents approximately 40–60 % of the uptake of $Hg^{2+}$ by proximal tubules (Zalups and Minor 1995). Pretreatment of rats with *para*-aminohippurate (PAH), which specifically inhibits members of the organic anion transporter (OAT) family (Hosoyamada et al. 1999; Sekine et al. 1997, 2006), significantly reduced the renal uptake of $Hg^{2+}$. Therefore, it appears that one or more OATs are involved in the basolateral uptake of $Hg^{2+}$. OAT1 (*SLC22A6*) and OAT3 (*SLC22A8*) have both been localized in the basolateral plasma membrane of proximal tubular epithelial cells (Breljak et al. 2016; Kojima et al. 2002; Motohashi et al. 2002), and thus, they are likely candidates for the uptake of mercuric species at the basolateral membrane of these cells. Indeed, findings

from MDCK II cells stably transfected with OAT1 showed that Cys and Hcy *S*-conjugates of $Hg^{2+}$ are transportable substrates of this carrier (Aslamkhan et al. 2003; Zalups and Ahmad 2004; Zalups et al. 2004). In addition, experiments using *Xenopus laevis* oocytes demonstrated that OAT3 plays a role in the uptake of Cys-*S*-Hg-*S*-Cys (Aslamkhan et al. 2003; Zalups et al. 2004). Taken together, these data indicate that OAT1 and OAT3 are likely involved in the basolateral uptake of select mercuric species.

Once mercuric ions gain access to the intracellular compartment of cells, they bind to protein and non-protein thiols such as GSH and metallothionein (MT). The binding of Hg to larger thiol-containing molecules such as MT likely yields a non-transportable form of Hg and thus facilitates retention of mercuric ions within the cell. Exposure to $Hg^{2+}$ has been shown to increase the mRNA expression of MT, which in turn leads to enhanced formation of Hg–MT complexes that are retained within renal epithelial cells (Zalups and Cherian 1992; Zalups et al. 1993; Zalups and Koropatnick 2000).

A small fraction of mercuric ions are transported out of proximal tubular cells without the use of a chelating agent (Bridges et al. 2011). However, the most efficient means of extracting mercuric ions from within target cells is through the use of a dithiol, metal chelator/complexing agent, such as 2,3-dimercapto-1-propanesulfonic acid (DMPS) or dimercaptosuccinic acid (DMSA; Fig. 2) (Aposhian 1983; Planas-Bohne 1981; Zalups and Bridges 2012). The ability of these two compounds to extract mercuric ions from target cells has been well characterized. The DMPS-mediated extraction of $Hg^{2+}$ has been shown to occur via a direct secretory process whereby mercuric ions move directly into the tubular lumen for subsequent elimination in urine (Diamond et al. 1988). DMPS is taken up at the basolateral membrane of proximal tubular cells via OAT1, OAT3, and the sodium-dependent dicarboxylate transporter (NaC1; *SCL13A2*) (Bahn et al. 2002; Burckhardt et al. 2002; Islinger et al. 2001; Rodiger et al. 2010), while DMSA has been shown to be taken up by NaC1 (Burckhardt et al. 2002). It has been hypothesized that once internalized, DMPS and DMSA form complexes with intracellular $Hg^{2+}$ (Zalups and Bridges 2012). These complexes appear to be transported across the luminal plasma membrane by MRP2, which is localized in the luminal plasma membrane of proximal tubular cells (Schaub et al. 1997, 1999). In vitro studies using inside-out membrane vesicles prepared from Sf9 cells transfected with human MRP2 provide direct evidence implicating MRP2 in the transport of both DMPS and DMSA-*S*-conjugates of $Hg^{2+}$ (Bridges et al. 2008a, b). Studies in Mrp2-deficient ($TR^{-}$) rats exposed to $HgCl_2$ and treated subsequently with DMPS or DMSA (Bridges et al. 2008a, b) also provided strong in vivo evidence supporting a role for MRP2 in the secretion of mercuric ions. MRP4 (*ABCC4*) is also localized in the apical membrane of proximal tubular cells, and although it has a substrate specificity that is similar to that of MRP2, it does not appear to be involved in the transport of DMPS *S*-conjugates of $Hg^{2+}$ (Bridges et al. 2013).

Secretion of mercuric ions at the luminal plasma membrane of proximal tubules may also occur via the breast cancer resistance protein (BCRP; *ABCG2*; Fig. 2). This carrier is localized in the apical plasma membrane of proximal tubular cells, and it has been shown to transport a wide variety of compounds (Leslie et al. 2005; Vlaming et al. 2009). A recent study using inside-out membrane vesicles from Sf9 cells overexpressing human BCRP

provided direct evidence demonstrating that Cys and DMPS *S*-conjugates of $Hg^{2+}$ are transportable substrates of BCRP (Bridges et al. 2015). In the same study, the disposition of mercuric ions in Bcrp-knockout rats was examined and the findings from these experiments demonstrated further the ability of Bcrp to transport mercuric ions.

## Hepatic transport of $Hg^{2+}$

Numerous in vivo studies in rats have shown that mercuric ions accumulate in hepatocytes following exposure to $HgCl_2$ (Bridges et al. 2008a, b, 2011, 2014, 2015; Oliveira et al. 2016, 2015; Zalups 1993a, b). When mercuric ions are presented to the sinusoidal membrane of hepatocytes, they are most likely bound to non-protein thiols and plasma proteins, such as albumin, ferritin, and γ-globulins. Since these mercuric complexes may be quite large, there are only a few mechanisms that may be involved in the uptake of $Hg^{2+}$ across the sinusoidal membrane of hepatocytes.

One of these mechanisms is endocytosis. Phagocytosis, pinocytosis, and receptor-mediated endocytosis have been shown to be involved in the uptake of molecules from sinusoidal blood into hepatocytes (Marbet et al. 2006; Rahner et al. 2000). Mercuric ions may be taken up into hepatocytes via an endocytic process mediated by albumin and/ or one of the iron-binding proteins. Thus, endocytosis of Hg–ferritin or Hg–albumin complexes may also serve as a route of entry of $Hg^{2+}$ into hepatocytes. Indeed, it has been suggested that ferritin may serve as a detoxifying protein due its ability to bind the cationic forms of a number of elements (Joshi et al. 1989).

Another method by which $Hg^{2+}$ may cross the sinusoidal membrane of hepatocytes may involve specific mechanisms of active transport in the plasma membrane. Various species of $Hg^{2+}$ may enter hepatocytes at the sinusoidal membrane via transporters that mediate the uptake of endogenous compounds that are similar structurally to certain mercuric species. OAT2 (*SLC22A7*) has been localized in the sinusoidal membrane of hepatocytes (Simonson et al. 1994), and it is involved in the uptake of organic anions into hepatocytes. As a member of the OAT family, OAT2 shares some similarities with OAT1 and OAT3, which have been shown to transport $Hg^{2+}$. However, there are also significant differences between these two carriers and OAT2 (Henjakovic et al. 2015), which may mean that OAT2 is not involved in the uptake of $Hg^{2+}$ into hepatocytes. In addition, OATP1B1 (*SLCO1B1*), OATP1B3 (*SLCO1B3*), and OATP2B1 (*SLCO2B1*) have been identified in the sinusoidal membrane of hepatocytes (Pfeifer et al. 2014) where they mediate the hepatic uptake of organic anions. A role for these carriers in the uptake of mercuric species has not been reported. Also, numerous amino acid transporters have been identified in the sinusoidal membrane of hepatocytes (Bode 2001; Kilberg 1982; Wagner et al. 2001), yet it is currently unclear if any of these transporters are involved in the uptake of mercuric species at the sinusoidal membrane.

The transport of $Hg^{2+}$ across the canalicular plasma membrane of hepatocytes has been studied extensively. A fraction of the $Hg^{2+}$ that is transported across the canalicular membrane into bile appears to be dependent upon the concentration of GSH within hepatocytes (Ballatori and Clarkson 1983, 1984, 1985a, b; Dutczak and Ballatori 1992; Zalups and Lash 1997). A reduction in GSH levels in rats exposed intravenously to $Hg^{2+}$ led

to an accumulation of mercuric ions within hepatocytes (Zalups and Lash 1997). These findings suggest that intracellular mercuric ions may bind with intracellular GSH to form G-*S*-Hg-*S*-G, which may be transported out of hepatocytes at the canalicular membrane. Possible mechanisms for this transport include MRP2 and BCRP, which are both present in the canalicular membrane of hepatocytes (Buchler et al. 1996; Maliepaard et al. 2001). Since MRP2 appears to utilize GSH as a co-substrate for other compounds (Akerboom et al. 1991; Keppler et al. 1997), it was hypothesized that this carrier may transport G-*S*-Hg-*S*-G, and possibly other species of $Hg^{2+}$. Recent studies using $TR^{-}$ rats, Mrp2- knockout mice, and inside-out membrane vesicles expressing MRP2 indicate that this carrier is capable of transporting $Hg^{2+}$ as a conjugate of Cys, DMPS, or DMSA (Bridges et al. 2008a, b, 2011, 2013). Similarly, studies using Bcrp-knockout rats and inside-out membrane vesicles expressing BCRP have recently implicated BCRP in the transport of various mercuric species (Bridges et al. 2015).

Additional transport proteins on the canalicular membrane that may be involved in the transmembrane transport of mercuric species into bile include the multidrug resistance protein 1 (MDR1; P-glycoprotein; *ABCB1*) and MRP3. Both of these carriers are localized in the canalicular membrane of hepatocytes and have been shown to transport a wide variety of substrates (Konig et al. 1999; Thiebaut et al. 1987). Given that the substrate specificity of these carriers is similar to that of MRP2 (Pfeifer et al. 2014), it is logical to postulate that MDR1 and MRP3 may be capable of mediating the transport of mercuric species across the canalicular membrane.

## Transport of $Hg^{2+}$ in the placenta

Despite previous claims that $Hg^{2+}$ does not cross the blood–placental barrier, several in vivo and in vitro studies have provided evidence for the transport and accumulation of $Hg^{2+}$ in placentas and fetuses (Ask et al. 2002; Inouye and Kajiwara 1990; Oliveira et al. 2015). A recent study in pregnant Wistar rats exposed intravenously to two different doses of $HgCl_2$ showed that the accumulation of mercuric ions in the placental and fetal organs was dependent on the time of exposure and the dose to which pregnant rats were exposed (Oliveira et al. 2015). Although maternal exposure to mercuric compounds during pregnancy can have significant detrimental effects on fetal development, the specific molecular mechanisms by which $Hg^{2+}$ is transported across placental syncytiotrophoblasts have not been well defined. Experiments using brush-border membrane vesicles from human placenta have implicated amino acid transporters in the placental uptake of $Hg^{2+}$ (Iioka et al. 1987). Considering the prevalence of amino acid transporters in the placenta (Jansson 2001; Kudo and Boyd 2002), it is possible that transportable forms of $Hg^{2+}$ may utilize one or more amino acid transporters to gain entry to the intracellular compartment of placental syncytiotrophoblasts. Candidates for this transport include System $b^{0,+}$, System L (LAT1; *SLC7A5*), and System $B^{0,+}$ ($ATB^{0,+}$; *SLC6A14*; Fig. 3). Additional studies are clearly needed to elucidate fully the mechanisms involved in the cellular uptake of mercuric species by placental syncytiotrophoblasts.

Currently, there are no data implicating a specific mechanism for the transport of $Hg^{2+}$ on the basolateral membrane of syncytiotrophoblasts. However, based on data from studies

using proximal tubular cells from the kidney, we suggest that carriers such as OAT4 (*SLC22A11*), System L (LAT2; *SLC7A8*), and System $B^{0,+}$ (Fig. 3) may be involved in the transport of mercuric ions across the basolateral membrane of syncytiotrophoblasts into the fetal capillaries.

## Transport of methylmercury

### Intestinal transport of methylmercury

As mentioned previously, humans are exposed to methylmercury ($CH_3Hg^+$) primarily through the ingestion of contaminated food. Therefore, it is critical that the mechanisms involved in the intestinal absorption of $CH_3Hg^+$ are understood thoroughly.

X-ray absorption spectroscopy (XAS) showed that the primary species of $CH_3Hg^+$ in muscle tissue of fish is a Cys *S*-conjugate of $CH_3Hg^+$ ($CH_3Hg$-*S*-Cys) (Harris et al. 2003). Therefore, following ingestion of fish, $CH_3Hg$- *S*-Cys will likely be present in the lumen of the intestine. Moreover, Cys *S*-$CH_3Hg$ also appears to enter the lumen of the intestine via secretion into bile (Norseth and Clarkson 1971). Even so, recent in vivo studies suggest that the components of ingested food have a significant influence on the ability of mercuric ions to be taken up by enterocytes (Vazquez et al. 2014). Ingested food has a high concentration of thiol-containing molecules, which may combine with ingested $CH_3Hg^+$ to form various thiol *S*-conjugates. GSH *S*-conjugates of $CH_3Hg$ ($CH_3Hg$-*S*-G) may also be present in the intestinal lumen (Urano et al. 1990). Experiments using ligated segments of rat intestine suggest that $CH_3Hg$-*S*-G in the intestinal lumen is broken down by γ-glutamyltransferase to form cysteinylglycine (CysGly) conjugates of $CH_3Hg^+$ ($CH_3Hg$-*S*-CysGly), which may be degraded further to yield $CH_3Hg$-*S*-Cys (Urano et al. 1990). The majority of $CH_3Hg^+$ taken up by enterocytes appears to be in the form of $CH_3Hg$-*S*-Cys (Vazquez et al. 2013, 2014). However, any $CH_3Hg$-*S*-CysGly that escapes degradation may be taken up into cells via one of the peptide transporters such as the oligopeptide transporter, PEPT1 (S*LC15A*), which is present in the luminal plasma membrane of enterocytes (Estudante et al. 2013). The remaining $CH_3Hg$-*S*-Cys may be taken up via intestinal amino acid transporters or organic anion transporters (Urano et al. 1990). Possible candidates for this transport include System $b^{0,+}$ and the organic anion transporting polypeptide (OATP2B1; *SLC22O*), which have both been localized in the apical membrane of enterocytes (Dave et al. 2004; Estudante et al. 2013; Klaassen and Aleksunes 2010; Tamai and Nakanishi 2013). Currently, there are no published data linking PEPT1, OAT2B1, or System $b^{0,+}$ to the intestinal uptake of any species of $CH_3Hg^+$.

$CH_3Hg^+$ gains access to the systemic circulation via carrier proteins in the basolateral membrane of enterocytes (Leaner and Mason 2002). MRP1, MRP3, MRP4, and MRP5 have been identified on the basolateral membrane of enterocytes (Estudante et al. 2013), and since conjugates of $CH_3Hg^+$ appear to be substrates of MRP2, it is possible that one or more MRPs are involved in export of mercuric species across the basolateral membrane of enterocytes. It has also been suggested that the efflux of $CH_3Hg^+$ at the basolateral membrane is regulated by the intracellular concentration of GSH (Foulkes 1993). Since some members of the MRP family require GSH as a co-substrate, it is feasible to suggest

that the export of $CH_3Hg^+$ across the basolateral membrane of enterocytes may involve one or more MRPs.

Alternatively, indirect evidence from isolated, perfused catfish intestines suggests that a neutral amino acid transporter is involved in the export of $CH_3Hg$-*S*-Cys at the basolateral membrane of enterocytes. Given that LAT2 is localized in the basolateral membrane of enterocytes (Dave et al. 2004) and because it appears to be involved in the transport of $CH_3Hg$-*S*-Cys in other cell types, this carrier may be involved in the export of mercuric species across the basolateral membrane of enterocytes.

## Transport of methylmercury in erythrocytes

Studies in Wistar rats exposed intravenously to a nonnephrotoxic dose of $CH_3Hg^+$ for 24 h have demonstrated that approximately 30 % of the administered dose of $CH_3Hg^+$ is detected in blood. Approximately 99 % of this $CH_3Hg^+$ is associated with erythrocytes, while the remaining 1 % is associated with the plasma fraction (Zalups and Bridges 2009). One possible explanation for this distribution could be the binding of $CH_3Hg^+$ to some component of the erythrocyte membrane. Indeed, studies in human erythrocyte ghosts demonstrated that the $Na^+$, $K^+$-ATPase is capable of binding seven molecules of $CH_3Hg^+$ while the $Mg^+$, $Ca^{+2}$-ATPase is capable of binding one molecule of $CH_3Hg^+$ (Berg and Miles 1979). Interestingly, binding of mercuric ions to the $Na^+$, $K^+$-ATPase has been shown to significantly inhibit the activity of this enzyme (Hahn et al. 1990).

Another possible explanation for this pattern of distribution is that mercuric ions are actively taken up into erythrocytes. Multiple transport systems appear to be involved in the uptake of $CH_3Hg^+$. It has been hypothesized that the primary mechanism involved in this transport is an organic anion transporter (Wu 1995, 1996). Additional mechanisms may include a D-glucose diffusive transporter, a cysteine-facilitated transporter, and/or a $Cl^-$ transporter (Wu 1995). Other studies showed that when erythrocytes were exposed to $CH_3Hg$-*S*-G in the presence of probenecid, the uptake of $CH_3Hg^+$ was reduced significantly. This finding suggests that one or more OATs may play a role in the uptake of mercuric ions into erythrocytes (Wu 1997). The transport of $CH_3Hg^+$ into erythrocytes is an area of study that clearly needs further characterization.

## Hepatic transport of methylmercury

Following absorption by the intestine, $CH_3Hg^+$ is delivered to the liver via portal blood. Little is known about the mechanisms by which $CH_3Hg^+$ is transported into hepatocytes at the sinusoidal membrane. In vivo studies in rats have shown that hepatic uptake and accumulation of $CH_3Hg^+$ is enhanced when Cys or GSH is either co-administered with or administered subsequently to $CH_3Hg^+$ (Thomas and Smith 1982). More recently, an in vitro study using cultured human hepatocytes (HepG2 cells) demonstrated that cellular uptake of $CH_3Hg^+$ occurs more rapidly when cells are exposed to $CH_3Hg^+$ as a conjugate of Cys than when exposed to $CH_3Hg^+$ alone (Wang et al. 2000). The actual mechanisms involved in this transport remain unknown.

The transport of $CH_3Hg^+$ across the canalicular membrane has been studied more extensively and is better defined. Findings from numerous studies indicate that transport of

$CH_3Hg^+$ from hepatocytes into the biliary canaliculus occurs in association with GSH (Ballatori and Clarkson 1982, 1983, 1985a; Refsvik 1982; Refsvik and Norseth 1975). This is not surprising since the majority of $CH_3Hg^+$ within hepatocytes appears to be bound to GSH (Omata et al. 1978). Interestingly, increased hepatocellular levels of GSH correspond to an increase in the excretion of GSH and $CH_3Hg^+$ into bile (Magos et al. 1978). In contrast, a reduction in the hepatic and biliary levels of GSH corresponds to a reduced accumulation of $CH_3Hg^+$ in liver (Refsvik 1978). Therefore, it seems that the intracellular concentration of GSH significantly impacts the hepatobiliary transport of $CH_3Hg^+$. It has been postulated that $CH_3Hg$-*S*-G, formed within hepatocytes, is transported across the canalicular membrane into bile. Since $CH_3Hg$-*S*-G is similar in shape to GSH, it is possible that this conjugate may utilize a GSH transporter in the canalicular membrane for export out of hepatocytes. Indeed, it has been suggested that a GSH transport system in the canalicular membrane plays a significant role in the hepatobiliary secretion of $CH_3Hg$-*S*-G (Dutczak and Ballatori 1994). MRP2, which is capable of transporting GSH, has since been identified in the canalicular membrane of hepatocytes (Ballatori and Dutczak 1994; Ballatori and Truong 1995; Fernandez-Checa et al. 1992, 1993; Garcia-Ruiz et al. 1992), and thus, it probably plays an important role in the export of $CH_3Hg^+$. Indeed, recent studies in $TR^-$ rats indicate that MRP2 is involved in the hepatobiliary elimination of mercuric ions following exposure to $CH_3Hg^+$ (Madejczyk et al. 2007; Zalups and Bridges 2009).

After secretion into bile, $CH_3Hg$-*S*-G appears to be broken down by γ-glutamyltransferase and cysteinylglycinase to yield $CH_3Hg$-*S*-Cys, which can be reabsorbed by cells lining the bile ducts as well as by enterocytes (Ballatori 1994; Dutczak and Ballatori 1992; Dutczak et al. 1991). Although the actual mechanisms involved in the uptake of mercuric ions along the biliary tree have not been determined, it is reasonable to hypothesize that $CH_3Hg$-*S*-Cys utilizes one or more amino acid transporters in order to gain access to cells. A number of various amino acid transporters have been identified in the biliary tree (Bode 2001; Wagner et al. 2001); however, the exact membrane localization of each carrier remains unknown.

## Transport of methylmercury in the brain

Similar to $Hg^{2+}$, methylmercury ($CH_3Hg^+$) does not exist as a free, unbound cation in biological systems (Hughes 1957), but rather, it is found conjugated to protein and non-protein thiols (Clarkson 1993; Simpson et al. 1973; Simpson 1961). Exposure to $CH_3Hg^+$ can cause significant adverse effects in the brain and central nervous system (CNS) (ATSDR 1999; WHO 2000). Clinical signs and symptoms of $CH_3Hg^+$ intoxication are associated with the death of neuronal cells in specific regions of the brain. In adults, the visual cortex and the cerebellum, specifically the cerebellar granule cells, appear to be most sensitive to the effects of $CH_3Hg^+$ (Aschner and Syversen 2005). Owing to the severe neurological toxicity associated with exposure to $CH_{3-}$ $Hg^+$, it is important to understand the cellular mechanisms that facilitate the movement of mercuric ions across the blood brain barrier. A number of studies have focused on the transport of $CH_3Hg^+$ in astrocytes, which are glial cells that provide support to the endothelial cells of the blood–brain barrier. Early studies utilizing homogenates of rat cerebrum demonstrated that GSH is the primary nonprotein thiol bound to $CH_3Hg^+$ (Thomas and Smith 1979). Subsequent studies in rats and primary cultures of bovine brain endothelial cells showed that co-administration of Cys with

$CH_3Hg^+$ increased the uptake of $CH_3Hg^+$ into capillary endothelial cells of the blood–brain barrier (Aschner and Clarkson 1988, 1989; Hirayama 1980; Roos et al. 2010). Interestingly, the uptake of $CH_3Hg^+$ into endothelial cells was inhibited significantly by the neutral amino acid, phenylalanine (Hirayama 1975, 1980, 1985; Thomas and Smith 1982). In vivo studies in rat brain (Aschner and Clarkson 1988) and in vitro studies in bovine cerebral capillary endothelial cells (Aschner and Clarkson 1989; Heggland et al. 2009) demonstrated that neutral amino acids are capable of inhibiting the uptake of $CH_3Hg$-*S*-Cys. These data collectively led to the hypothesis that $CH_3Hg$-*S*-Cys is a transportable substrate of one or more neutral amino acid transporters in the luminal membrane of capillary endothelial cells. It was suggested that the structural similarities between $CH_3Hg$-*S*-Cys and methionine (Jernelov 1973; Landner 1971) serve as an important factor in the transport of $CH_3Hg^+$ across the blood–brain barrier. One possible mechanism for this transport is the amino acid carrier, System L (Wagner et al. 2001).

System L is a heterodimeric protein, comprised of a light chain (either LAT1, *SLC7A5*, or LAT2, *SLC7A8*) and a heavy chain (4F2hc, *SLC3A2*) bound together with a disulfide bond (Chillaron et al. 2001; Wagner et al. 2001). LAT1 and LAT2 have been localized in the apical and basolateral plasma membranes, respectively, of endothelial cells lining the blood–brain barrier (Betz and Goldstein 1978). In addition, LAT1 and LAT2 have also been identified in cultured glial cells (Kim et al. 2004). System L is capable of transporting a broad range of neutral amino acids such as methionine (Met) and leucine (Leu) (Oldendorf 1973). Since $CH_3Hg$-*S*-Cys and Met are similar in shape and size (Bridges and Zalups 2010) and because Met is a substrate of System L, it was hypothesized that $CH_3Hg$-*S*-Cys may also be a substrate for System L. Indeed, in vivo and in vitro studies have provided strong evidence supporting the idea that $CH_3Hg$-*S*-Cys is a transportable substrate of System L (Aschner et al. 1990, 1991; Kerper et al. 1992; Simmons-Willis et al. 2002; Zimmermann et al. 2013). Studies using epithelial cells from hamster ovary (CHOk1) demonstrated that overexpression of LAT1 enhances uptake of $CH_3Hg$-*S*-Cys into cells. When the expression of LAT1 was reduced with small interference RNA (siRNA), a corresponding reduction in the intracellular burden of $CH_3Hg^+$ was observed, suggesting that $CH_3Hg$-*S*-Cys is a transportable substrate of LAT1 (Yin et al. 2008). Site-directed mutagenesis of LAT1 has been shown to cause a reduction in the cellular uptake of $CH_3Hg^+$, providing additional evidence for the hypothesis that $CH_3Hg$-*S*-Cys is a substrate of LAT1 (Boado et al. 2005). Taken together, these data provide strong support for the hypothesis that $CH_3Hg$-*S*-Cys is taken into cells via one or both isoforms of System L. Interestingly, a recent study indicated that co-administration of methionine and $CH_3Hg^+$ enhanced motor impairments in mice compared with administration of $CH_3Hg^+$ alone (Zimmermann et al. 2014). This finding suggests that a trans-stimulatory phenomenon may occur whereby the presence of additional substrate enhances the activity of the transporter so that more substrate, including $CH_3Hg^+$, is taken up by the carrier. Indeed, the activities of System L and System $b^{0,+}$ have been shown previously to be enhanced by trans-stimulation with amino acids (Bridges et al. 2004; Fraga et al. 2002; Segel et al. 1988). It is also important to note that Hcy *S*-conjugates of $CH_3Hg^+$ ($CH_3Hg$-*S*-Hcy) may also be substrates of System L (Mokrzan et al. 1995).

## Renal transport of methylmercury

Although $CH_3Hg^+$ does not accumulate in the kidney to the same degree as $Hg^{2+}$, this form of Hg still accumulates in proximal tubular cells at significant levels and is capable of inducing significant detrimental effects (Friberg 1959; Magos et al. 1985; Magos and Butler 1976; Magos et al. 1981; McNeil et al. 1988; Norseth and Clarkson 1970a, b; Prickett et al. 1950). The majority of published evidence indicates that $CH_3Hg$-*S*-Cys is the primary species of $CH_3Hg^+$ taken up by renal epithelial cells. It has been proposed that $CH_3Hg^+$, as a conjugate of GSH, enters the proximal tubular lumen where γ-glutamyltransferase and cysteinylglycinase act on the GSH molecule to yield $CH_3Hg$-*S*-Cys (Berndt et al. 1985; de Ceaurriz and Ban 1990; Di Simplicio et al. 1990; Gregus et al. 1987; Mulder and Kostyniak 1985; Naganuma et al. 1988; Tanaka et al. 1990, 1991, 1992; Yasutake et al. 1989).

Given that $CH_3Hg$-*S*-Cys is similar in shape and size to methionine, it is reasonable to suggest that $CH_3Hg$-*S*-Cys can be taken up into proximal tubular cells via transport mechanisms that mediate the uptake of methionine. Indeed, data from an in vivo study utilizing oocytes from *Xenopus laevis* indicate that the amino acid transporter, System $B^{0,+}$, is capable of mediating the transport of $CH_3Hg$-*S*-Cys or a $CH_3Hg^+$ *S*-conjugate of Hcy ($CH_3Hg$-*S*-Hcy) (Bridges and Zalups 2006). System $B^{0,+}$ is localized in the luminal plasma membrane of proximal tubular cells (Gonska et al. 2000) and mediates the $Na^+$-dependent transport of many neutral and cationic amino acids, including methionine (Nakanishi et al. 2001; Sloan and Mager 1999). It is interesting to note that the substrate specificity of System $B^{0,+}$ is similar to that of System $b^{0,+}$, which has been shown to mediate the $Na^+$-independent transport of Cys-*S*-Hg-*S*-Cys and Hcy-*S*-Hg-*S*-Hcy (Bridges et al. 2004; Bridges and Zalups 2004).

$CH_3Hg^+$ present in peritubular blood may be taken up into renal tubular cells via mechanisms on the basolateral membrane (Tanaka et al. 1992). Studies utilizing cultured renal epithelial cells indicate that OAT1, which is localized in the basolateral membrane of proximal tubular epithelial cells (Kojima et al. 2002; Motohashi et al. 2002), mediates the uptake of Cys-, Hcy-, and NAC-*S*-conjugates of $CH_3Hg^+$ (Koh et al. 2002; Zalups and Ahmad 2005a, b, c).

Once mercuric ions gain access to the intracellular compartments of cells, they tend to form strong bonds with intracellular thiols. Therefore, in order to facilitate the export of mercuric ions from within cells, metal chelators/ complexing agents must be utilized. The ability of the metal chelators, DMPS and DMSA, to extract mercuric ions from cells following exposure to $CH_3Hg^+$ has been well documented (Aposhian 1983; Aposhian et al. 1992). However, the mechanisms by which this extraction occurs have been identified only recently. Data from in vivo studies using $TR^-$ rats exposed to $CH_3Hg^+$ and treated subsequently with NAC, DMPS, or DMSA indicate that MRP2 plays an important role in the transport of $CH_3Hg^+$ from within proximal tubular cells into the tubular lumen (Madejczyk et al. 2007; Zalups and Bridges 2009). Even in the absence of a metal chelator, MRP2 has been shown to play a role in the renal handling of $Hg^{2+}$ (Bridges et al. 2011). More direct evidence was obtained from studies using membrane vesicles isolated from kidneys of $TR^-$ rats. Data from this study suggest that $CH_3Hg$-*S*-NAC is a transportable substrate of MRP2 (Madejczyk et al. 2007). Additional experiments using inside-out membrane vesicles from Sf9 cells

transfected with human MRP2 provide evidence indicating that MRP2 is capable of mediating the transport of DMPS- and DMSA-*S*-conjugates of $CH_3Hg^+$ (Zalups and Bridges 2009). Taken together, the data from these studies provide strong support for the hypothesis that MRP2 mediates the cellular export of mercuric ions following exposure to $CH_3Hg^+$ with subsequent chelation therapy.

## Transport of methylmercury in the placenta

The deleterious effects of $CH_3Hg^+$ on fetal development have been recognized widely as one of the most serious toxicological consequences of $CH_3Hg^+$ exposure (Amin-Zaki et al. 1974; Davidson et al. 2008; Harada 1978, 1995; Inouye and Kajiwara 1988; Kajiwara and Inouye 1986, 1992; Matsumoto et al. 1965). Following maternal exposure to $CH_3Hg^+$, mercuric ions are taken up readily by the placenta and accumulate subsequently in both placental and fetal tissues (Ask et al. 2002; Inouye and Kajiwara 1988; Inouye et al. 1985). Despite the fact that fetal exposure to $CH_3Hg^+$ is highly significant clinically, little is known about the mechanism(s) by which mercuric ions are taken up and transported across the placenta. In vivo studies (Kajiwara et al. 1996) have shown that $CH_3Hg^+$ is transported across the rat placenta by a neutral amino acid carrier in a time- and dose-dependent manner. Interestingly, co-administration of $CH_3Hg^+$ with methionine increased the placental burden of $CH_3Hg^+$. It was proposed that this increase in uptake may be the result of the intracellular conversion of methionine to Cys, which may subsequently combine with $CH_3Hg^+$ to form a transportable species of $CH_3Hg^+$, i.e., $CH_3Hg$-*S*-Cys. This conjugate may utilize a neutral amino acid carrier such as System L in order to gain access to placenta trophoblasts. Since the two isoforms of System L, LAT1 and LAT2, have been shown to mediate the transport of $CH_3Hg$-*S*-Cys in astrocytes and endothelial cells of the blood–brain barrier (Aschner et al. 1990; Kerper et al. 1992; Mokrzan et al. 1995; Simmons-Willis et al. 2002), it is logical to hypothesize that this same carrier may also be involved in the transport of $CH_3Hg$-*S*-Cys across the placenta. In the placenta, LAT1 is localized in the apical (maternal) plasma membrane of trophoblasts, while LAT2 is found in the basolateral (fetal) membrane (Kudo and Boyd 2002). A number of other carrier systems (e.g., amino acid, organic anion) have been identified in the placenta (Leazer and Klaassen 2003), and although the roles of these other transporters in the transport of $CH_3Hg^+$ have not been examined, they should be considered as possible mechanisms for this transport.

The mechanisms on the basolateral membrane of trophoblasts that mediate the uptake of mercuric ions from fetal circulation into the placenta have not yet been identified with certainty. One possible mechanism is OAT4, which has been localized in the basolateral membrane of placental trophoblasts (Cha et al. 2000; St-Pierre et al. 2000). Since other members of the OAT family have been shown to transport mercuric ions, it is possible that OAT4 may also be capable of mediating the transport of mercuric species. To date, the ability of OAT4 to transport mercuric ions has not been reported.

Recently, the ability of different chelators to extract mercuric ions from placental and fetal tissues was examined. In pregnant rats exposed to $CH_3Hg^+$, treatment with NAC, DMPS, or DMSA has been shown to facilitate the extraction of mercuric ions from fetal and placental tissues (Aremu et al. 2008; Bridges et al. 2009). As mentioned above, OAT4 may mediate

the basolateral uptake of mercuric species into trophoblasts. MRP2, which is localized in the apical membrane of placental trophoblasts (St-Pierre et al. 2000), may mediate the export of mercuric ions from within trophoblasts into the maternal circulation. Currently, there are no direct data to support these theories.

## Conclusions

Every effort has been made to summarize the current body of literature related to the transport of mercuric ions in key target organ systems and tissues. Despite the growing body of literature pertaining to the handling of various species of mercury within the body, there are numerous gaps in our knowledge. A great deal of research is still required in order to understand more completely the mechanisms involved in the movement of mercuric ions across cellular plasma membranes. A thorough understanding of the mechanisms participating in the transport of mercuric ions at the cellular and molecular levels may lead to advances in treatment regimens for patients exposed to or intoxicated by mercury.

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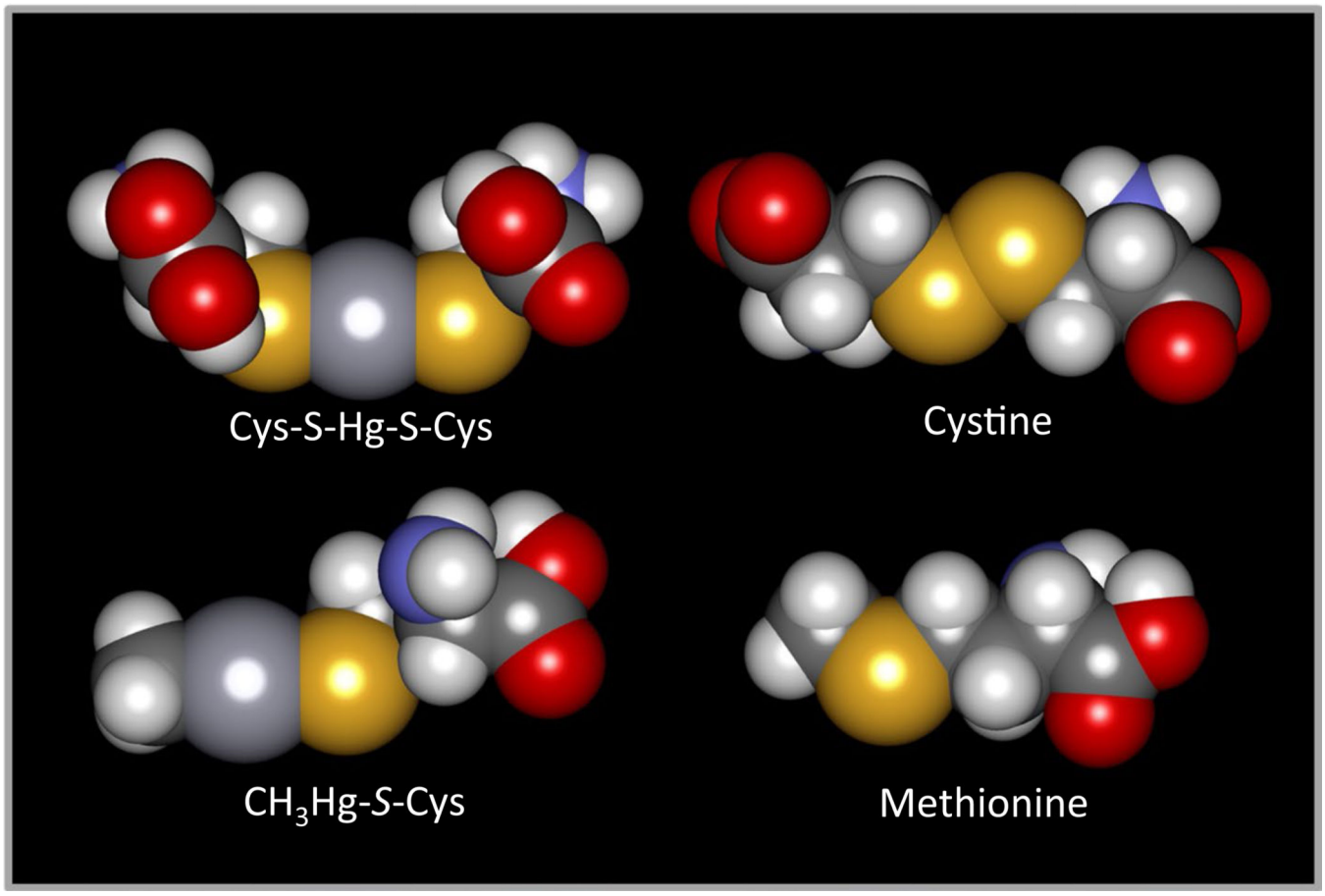


**Fig. 1.**

Space-fill models of Cys *S*-conjugates of $Hg^{2+}$ and $CH_3Hg^+$ compared with the amino acids, cystine, and methionine. The Cys *S*-conjugate of $Hg^{2+}$ (Cys-*S*-Hg-*S*-Cys) is similar in shape and size to cystine, while the Cys *S*-conjugate of $CH_3Hg^+$ ($CH_3Hg^+$-*S*Cys) is similar to methionine. Owing to these similarities, it has been hypothesized that Cys- *S*-Hg-*S*-Cys and Cys-*S*-$CH_3Hg^+$ are transportable substrates of carrier proteins that mediate the transport of cystine and methionine, respectively

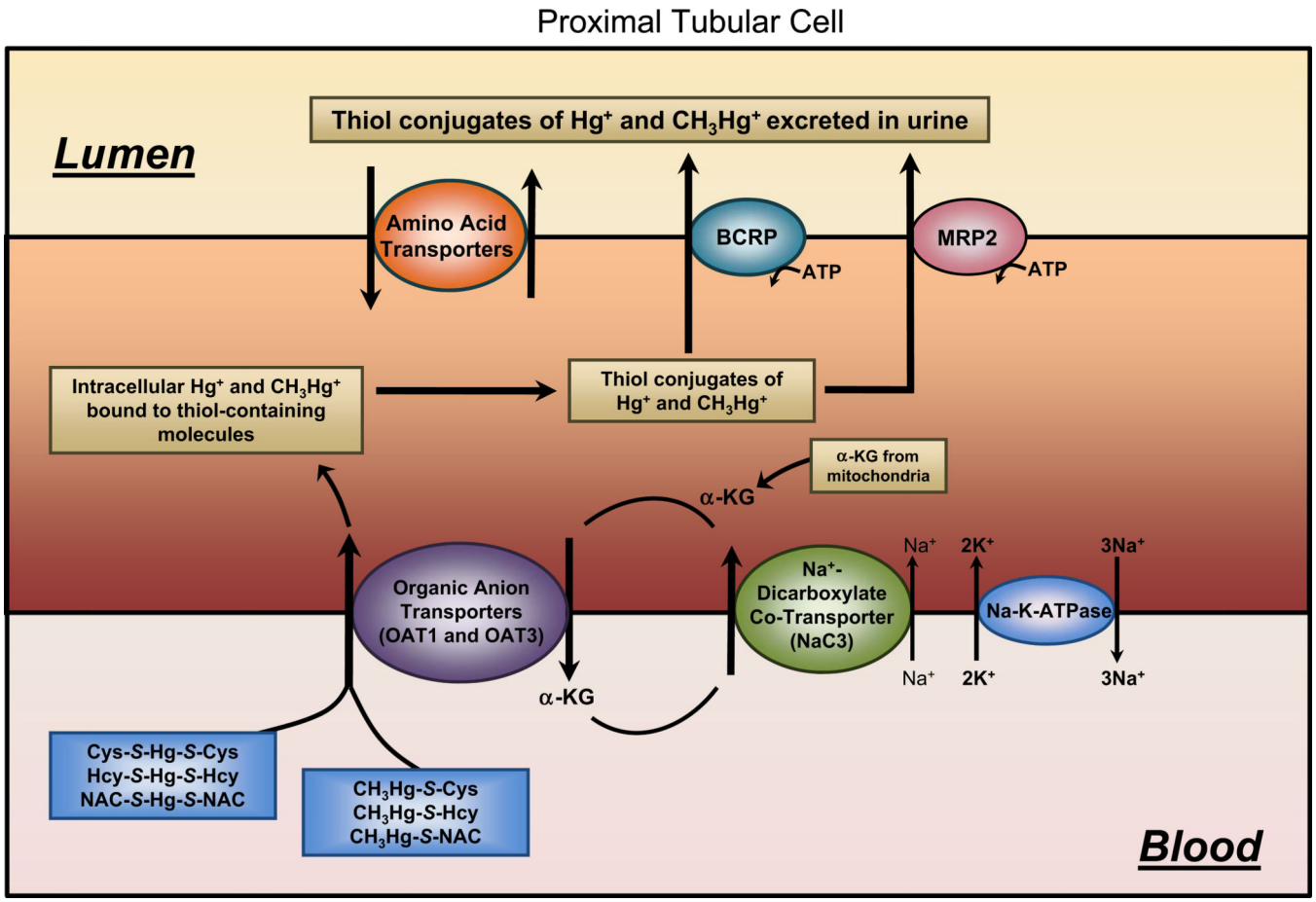


**Fig. 2.**

Diagram of a proximal tubular cell outlining the mechanisms involved in the uptake and export of $Hg^{2+}$ and $CH_3Hg^+$. At the luminal plasma membrane of proximal tubular cells, it appears that amino acid transporters are the primary mechanisms by which mercuric ions are taken up into cells. At the basolateral membrane, organic anion transporters (OAT) appear to be primarily involved in this uptake. Mercuric species may be secreted from proximal tubular cells into the tubular lumen via the actions of the breast cancer resistance protein (BCRP) or the multidrug resistance-associated protein (MRP2) located on the luminal plasma membrane

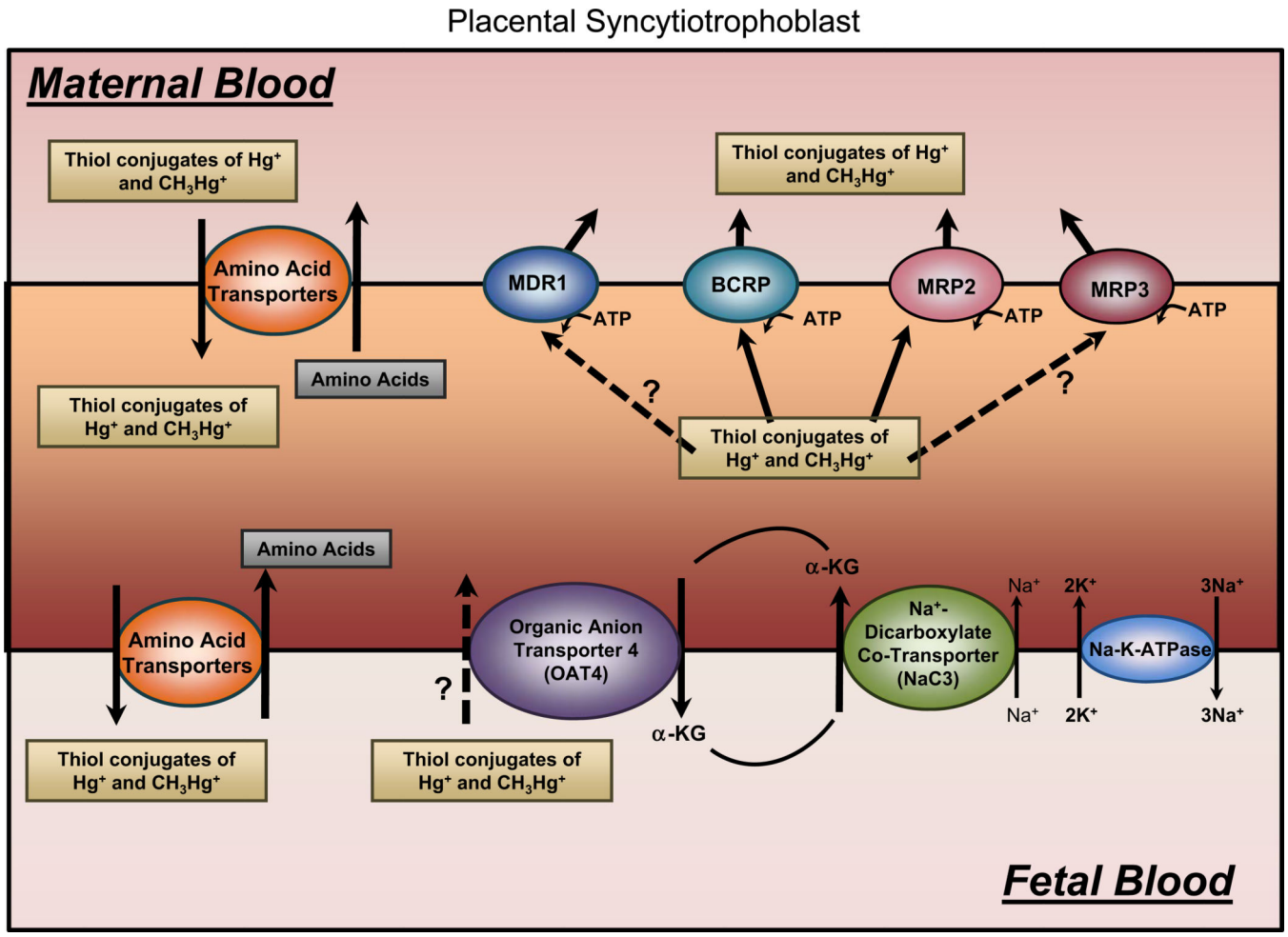


**Fig. 3.**

Diagram of a placental syncytiotrophoblast outlining the mechanisms potentially involved in the uptake and export of $Hg^{2+}$ and $CH_3Hg^+$. Mercuric species may be taken up by placental syncytiotrophoblasts via amino acid transporters on the apical (maternal) side of the cell. Conjugates of $Hg^{2+}$ and $CH_3Hg^+$ may remain in the intracellular compartment of the cell, or they may be exported into the interstitial space surrounding the fetal circulation via amino acid transporters on the basolateral side. In order to eliminate mercuric species from placental and fetal tissues, mercuric ions may be taken up by the organic anion transporter (OAT) 4 located in the basolateral membrane. Export at the luminal membrane may involve the multidrug resistance protein (MDR1), the breast cancer resistance protein (BCRP), and/or the multidrug resistance-associated protein 2 (MRP2) and MRP3