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Review

Methylmercury: A potential environmental risk factor contributing to epileptogenesis

Yukun Yuan *

Department of Pharmacology and Toxicology, Michigan State University, East Lansing, MI 48824, USA

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ABSTRACT

Epilepsy or seizure disorder is one of the most common neurological diseases in humans. Although genetic mutations in ion channels and receptors and some other risk factors such as brain injury are linked to epileptogenesis, the underlying cause for the majority of epilepsy cases remains unknown. Gene–environment interactions are thought to play a critical role in the etiology of epilepsy. Exposure to environmental chemicals is an important risk factor. Methylmercury (MeHg) is a prominent environmental neurotoxicant, which targets primarily the central nervous system (CNS). Patients or animals with acute or chronic MeHg poisoning often display epileptic seizures or show increased susceptibility to seizures, suggesting that MeHg exposure may be associated with epileptogenesis. This mini-review highlights the effects of MeHg exposure, especially developmental exposure, on the susceptibility of humans and animals to seizures, and discusses the potential role of low level MeHg exposure in epileptogenesis. This review also proposes that a preferential effect of MeHg on the inhibitory GABAergic system, leading to disinhibition of excitatory glutamatergic function, may be one of the potential mechanisms underlying MeHg-induced changes in seizure susceptibility.

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1. Introduction

Epilepsy, a disease defined by recurrent spontaneous seizures, is one of the most common neurological disorders in humans. It affects 2.3 million Americans and approximately 50 million peoples worldwide with a prevalence rate about 0.5–1% (Hauser et al., 1993; Olafsson et al., 2005). Although genetic mutations in ion channels or ligand-gated receptors (for review, see Lerche et al., 2001; Hirose, 2006; Graves, 2006; Catteral et al., 2010; Mantegazza et al., 2010; Macdonald et al., 2010) and other risk factors such as head trauma, stroke, infections, brain tumor, brain developmental defects and toxins (for review, see Frey, 2003; D'Ambrosio and Perucca, 2004; Singh and Prabhakar, 2008; Lowenstein, 2009; Prince et al., 2009) have been linked to epileptogenesis, the underlying cause for most epilepsy cases remains to be identified. It is generally believed that interactions of environmental factors with genetic and other intrinsic factors play an important role in the etiology of seizures or epilepsy (Kjeldsen et al., 2002; Bener et al., 2006; Todorova et al., 1999, 2006; Nakayama, 2009; Vestergaard and Christensen, 2009; Stewardt, 2010). Exposure to some environmental chemical pollutants such as ozone (Escalante-Membrillo and Paz, 1997), lead (Krishnamoorthy et al., 1993; Arrieta et al., 2005), nickel (Denays et al., 2005), manganese (Hernandez et al., 2003), teimethyltin (Nishimura et al., 2001),

* Correspondence address: Department of Pharmacology/Toxicology, B307A Life Science Building, Michigan State University, East Lansing, MI 48824-1317, USA. Tel.: +1 517 353 2970; fax: +1 517 353 8915.
E-mail address: yuanyuku@msu.edu.

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organophosphates (McDonough and Shin, 1997; Solberg and Belkin, 1997; Myhrer, 2007) or domoic acid (Tiedeken and Ramsdell, 2007; Stewardt, 2010) has been shown to initiate or promote the development of seizures or epilepsy. Clinical and epidemiological studies suggest that methylmercury (MeHg), a prominent environmental contaminant, is an important environmental risk factor contributing to epileptogenesis. This mini-review will outline the effects of acute and chronic MeHg exposure, particularly developmental exposure, on the susceptibility of the brain to seizures or epilepsy based on currently available data and briefly discuss the potential mechanisms underlying MeHg-induced changes in seizure susceptibility.

2. Acute or chronic MeHg exposure causes epileptic seizures in human

Although the primary symptoms and signs of acute and chronic MeHg poisoning typically include visual functional disturbances (concentric constriction of the visual fields and reduced visual acuity), paresthesia, ataxia, dysarthia, and hearing impairment (Hunter and Russell, 1954; Takeuchi et al., 1959, 1962; Kurland et al., 1960; Tokuomi and Okajima, 1961; Bakir et al., 1973; Rustam and Hamdi, 1974; Chang, 1980; Nierenberg et al., 1998; Weiss et al., 2002; Clarkson et al., 2003), patients also often present with seizures or epilepsy (Harada, 1968, 1979, 1995; Marsh et al., 1987). In the Minamata Bay area of Japan, a region contaminated heavily with MeHg during 1950s, 8–9% of patients who suffered from Minamata disease (MD, a neurological disorder caused by chronic MeHg poisoning) experienced epileptic seizures. The types of epilepsy seen in MD patients were often atypical, many were clonic seizures with or without effects on consciousness. In Goshonoura town, a nearby area that was also contaminated by the same source of MeHg but much less heavily compared with Minamata area, 2.86% of MD patients developed epilepsy. In contrast, only 0.8% of the age- and sex-matched controls in a non-MeHg-contaminated area exhibited epilepsy (Harada, 1979). Thus, the frequency of epilepsy in MD patients of the Minamata area was >10 fold higher than that of age- and sex-matched controls in the non-MeHg-contaminated area. In agreement with the increased prevalence rate of behavioral epileptic seizures, electroencephalograph (EEG) examination of MD patients also confirmed a high rate of EEG abnormality. In 106 MD patients with or without complaints of seizures, EEG examination showed abnormalities in 66 (62.2%) patients, of which 22 (33.3%) cases exhibited paroxysmal discharges (Harada, 1979).

Consistent with the notion that the developing brain is particularly sensitive to MeHg, the frequency of convulsive seizures was much higher in children with congenital MD, an infantile form of MD with high incidence of cerebral palsy-like symptoms resulting from prenatal MeHg exposure (Harada, 1979). Convulsive seizures were observed in over 50% of congenital MD patients (11 of 22 cases in the Minamata district during 1955–1957 or 5 of 6 cases in the Minamata Bay area during 1955–1962). The hair mercury content of children with congenital MD was 40.3 ± 30.3 μg/g, whereas the hair mercury content of age-matched control individuals was <7 μg/g (Harada, 1968, 1979). Similarly, an increased incidence of convulsive seizures was observed in children with prenatal and postnatal MeHg exposure in an episode of acute MeHg poisoning in Iraq (Marsh et al., 1987). The increase in seizure incidence depended on MeHg exposure levels: when the maximum mercury content in maternal head hair was <75 ppm, none of the 53 children examined had seizures; when the maximum maternal hair mercury contents were 75–150 ppm, 1 of 6 (16.7%) children experienced seizures; when the maximum hair mercury content was >150 ppm, 6 of the 22 (27.3%) children developed seizures. Thus, the incidence of convulsive seizures among children with developmental MeHg exposure, in both Japan and Iraq MeHg poisoning episodes, was strongly associated with levels of MeHg exposure. In 1969, four children from a New Mexico family with pre- and/or postnatal exposure to MeHg following a 3-month long consumption of MeHg-contaminated pork developed severe neurological disorders (Snyder, 1971; Davis et al., 1994). Three of the four children developed seizures at one point during a 22-years follow-up study (Davis et al., 1994). Epileptoform abnormalities of EEG were observed in the two youngest children with behavioral seizures (Synder, 1971; Brenner and Synder, 1980). The total mercury (Hg) content in the cerebral cortex from one of the children who was exposed to MeHg postnatally and died 22 years later remained 50 times higher than those of the control patient (~1.595 vs 0.038 μg/g), confirming that epileptic seizures in these children were associated with developmental MeHg exposure. In contrast, their parents did not develop any overt symptoms or signs of MeHg poisoning in spite of being exposed to MeHg over same time period. Similar phenomena were also observed in parents of congenital MD patients in Japan (Harada, 1979) and children with prenatal MeHg exposure in Iraq (Marsh et al., 1987). In both Japan and Iraq cases, infants with prenatal MeHg exposure displayed overt clinical symptoms and signs of neurotoxicity while their mothers remained asymptomatic. Clearly, these data suggest that developing brains are particularly susceptible to MeHg-induced epileptic seizures.

A common theme in these MeHg poisoning episodes described above is that convulsive seizures seen in patients in Minamata Bay, Iraq, and the New Mexico family occurred after acute or chronic exposure to high levels of MeHg. Therefore, it is possible that the increased incidence rate of epilepsy or seizures in patients with MeHg poisoning could simply be secondary to MeHg-induced severe brain injury. The question then is whether chronic exposure, particularly developmental exposure, to low levels of MeHg alters the susceptibility of humans to seizures or epilepsy. This is particularly important because humans today are exposed to MeHg primarily through the consumption of MeHg-contaminated fish and seafood.

One of the main public health concerns surrounding chronic exposure to low levels of MeHg through the consumption of contaminated fish and seafood is the potential developmental neurotoxicity of MeHg in young children because the developing brains are highly vulnerable to this neurotoxicity (Harada, 1979; Marsh et al., 1987; Davis et al., 1994). To address this issue, several epidemiological studies have been carried out in Canada (McKeown-Eyssen et al., 1983), New Zealand (Crump et al., 1998), the Faroe Islands (Grandjean et al., 1997, 1998), Amazonian Basin (Grandjean et al., 1999), French Guiana (Cordier et al., 2002), the Republic of Seychelles (Davidson et al., 1998, 2000, 2006; Myers et al., 2003, 2009) and Tohoku district of Japan (Suzuki et al., 2010) in an attempt to study the effects of developmental MeHg exposure from fish consumption on child neurodevelopment. Results obtained from studies in Canada, New Zealand, the Faroe Islands, Amazonian Basin, French Guiana and Tohoku district of Japan suggest that there is a positive association between prenatal MeHg exposure and subtle neurological and/or neuropsychological deficits. In the Faroe Islands, extensive neuropsychological tests of 917 7-year-old children revealed that prenatal MeHg exposure was associated with deficits in cognitive function including primarily attention, language and memory, and to a lesser extent in visual-spatial and motor functions (Grandjean et al., 1997, 1998). However, similar extensive epidemiological studies in the Republic of Seychelles (Myers et al., 1995, 1997, 2003; Davidson et al., 1998, 2000; Axtell et al., 2000) failed to find any significant adverse effect from ocean fish consumption on child neurodevelopment. The exact reasons for the apparent disagreement between the two major cohort epidemiological studies remain unclear, but some possible confounding variables such as different types of fish

consumed by the two different populations and beneficial effects of the nutrients from fish consumption may contribute to the divergent outcomes (for review, see Counter and Buchanan, 2004; Clarkson and Magos, 2006; Grandjean et al., 2010; Grandjean and Herz, 2011). Regardless of the disagreement between the two major cohort studies, none of these studies has reported an increased incidence of childhood seizures or epilepsy. However, no information is available to indicate that childhood seizures such as neonatal seizures and febrile seizures or epilepsy were included as a specific endpoint in these studies. In fact, children with clinically diagnosed epilepsy or neonatal seizures were pre-excluded from further analyses in both the Foroe Islands (Grandjean et al., 1997, 1998) and Seychelles studies (Marsh et al., 1995). From this point of view, the epidemiological data appear to be insufficient at present to draw any definite conclusion about the relationship between chronic exposure to low levels of MeHg and seizures (neonatal seizures or febrile seizures) or epilepsy (childhood or adult) in humans. Interestingly, an elevated rate of male cerebral palsy hospitalization has been shown in the Great Lakes communities that were associated with historic use and natural resource of mercury (Gibertson, 2004, 2009). It is known that epilepsy is highly associated with cerebral palsy; 15–60% of children with cerebral palsy also suffer epilepsy (Kwong et al., 1998; Gururaj et al., 2003). Thus, theoretically, the incidence of epilepsy in these Great Lakes areas should be higher as well. However, no such data are available yet to support this assumption.

3. Developmental MeHg exposure increases seizure susceptibility in animal models

Consistent with findings in epidemiological and clinical studies, developmental MeHg exposure also alters neuronal excitability and susceptibility to seizures in different animal models. Szász et al. (1999, 2002) showed that exposure of rats to low levels of MeHg (0.375 mg/kg body weight/day) during the entire mating, gestation and lactation period significantly enhanced epileptogenicity in their offspring compared with those of age-matched controls in response to chemoconvulsive agent 3- or 4-aminopyridine. Electrocorticographic examinations showed a significant increase in the frequency and summated duration of paroxysmal activity and probability of generalized seizures in MeHg-treated animals at both postnatal day 28 (PND28) and PND90; epileptic activity spread over the whole cortical surface of the brains. These data suggest that pre- and postnatal MeHg exposure significantly increased the susceptibility of both young and adult animals to seizures and facilitated propagation of epileptiform activity (Szász et al., 1999, 2002). Similar effects were also seen in the offspring of rats that were exposed to inorganic mercury (Hg^{2+}) under similar experimental conditions, although the effect of Hg^{2+} on epileptogenicity appeared to be long-lasting (Szász et al., 2002). In agreement with these findings, prenatal and postnatal exposure of rats to MeHg using the same exposure paradigm as described above resulted in a decreased threshold for evoking excitatory postsynaptic potentials and spikes in neurons of neocortical slices, suggesting an increase in neuronal excitability (Világi et al., 2000). Furthermore, a single injection of 0, 6, 8 or 12 mg/kg body weight MeHg to pregnant mice on Day 10 of gestation resulted in a significantly reduced threshold to seizures induced by the convulsive agent flurothyl in the offspring (Su and Okita, 1976). Similarly, exposure of pregnant mice to a single dose of MeHg at 6 or 8 mg/kg body weight on Day 12 of gestation significantly increased the susceptibility of mouse offspring to audio-induced seizures (Menashi et al., 1982). Thus, these data suggest that prenatal MeHg exposure, regardless of whether it is single exposure at higher levels or chronic exposure at low levels, can alter the susceptibility of animals to seizure induction.

Theoretically, MeHg-induced changes in seizure susceptibility should also occur in animals following postnatal exposure, similar to children with MeHg poisoning (Harada, 1968, 1979; Snyder, 1971; Davis et al., 1994; Marsh et al., 1987). Using field potential recording techniques we have recently shown that early postnatal exposure of rats to low levels of MeHg caused a time-dependent increase in epileptiform activity of neurons in cortical slices (Dasari and Yuan, 2010). MeHg also increased sensitivity of cortical neurons to GABAergic antagonist-induced epileptiform activity and significantly reduced threshold for neuronal excitation, suggesting an increased neuronal excitability or hyperexcitibility. These data imply that postnatal MeHg exposure will also increase the susceptibility of animals to seizures. Thus, developmental MeHg exposure, either prenatal or postnatal or both, could be a potential risk factor contributing to the etiology of epileptic seizures.

4. Preferential effects of MeHg on GABAergic function may primarily contribute to MeHg-induced increases in seizure susceptibility

A critical gap in our understanding is how MeHg exposure alters the susceptibility of humans and animals to seizures or epilepsy. MeHg has the potential to interact with a variety of membrane proteins including enzymes, transporters, ion channels and receptors to induce a broad spectrum of neurotoxicity via specific and/or nonspecific actions at multiple target sites due partly to its high affinity and reactivity with –SH groups (for review, see Chang, 1980; Atchison and Hare, 1994; Shafer, 2000; Castoldi et al., 2001; Allen et al., 2002; Limke et al., 2004b; Atchison, 2005; Aschner and Aschner, 2007; Aschner et al., 2007). Thus, we predict that multiple mechanisms contribute to MeHg-induced changes in seizure or epilepsy susceptibility.

Channelopathies or mutations in ion channels including voltage-gated Na^+, Ca^{2+}, K^+ and Cl^- channels and receptors for acetylcholine and γ-aminobutyric acid (GABA) are associated with a variety of seizure disorders or epilepsy syndromes (for review, see Lerche et al., 2001; Hirose, 2006; Graves, 2006; Catteral et al., 2010; Mantegazza et al., 2010; Macdonald et al., 2010). Interestingly, MeHg affects voltage-gated Ca^{2+} channels (Shafer and Atchison, 1991; Sakamoto et al., 1996; Leonhardt et al., 1996; Sirois and Atchison, 2000; Shafer et al., 2002; Peng et al., 2002a,b), voltage-gated Na^+ and K^+ channels (Shrivastav et al., 1976; Quandt et al., 1982; Shafer and Atchison, 1992; Shafer et al., 2002; Yuan et al., 2005) and ligand-gated ion channels such as acetylcholine receptors (Von Burg et al., 1980; Quandt et al., 1982; Limke et al., 2004a; Roda et al., 2008), glutamate receptors (Yuan and Atchison, 1995, 1999, 2007) and $GABA_A$ receptors (Arakawa et al., 1991; Fonfría et al., 2001; Yuan and Atchison, 1997, 2003; Herden et al., 2008). It might be puzzling if blockade by MeHg of voltage-gated Ca^{2+} or Na^+ channels results in neuronal hyperexcitability because the opposite effects (reduced neuronal excitability) are expected based on the roles of voltage-gated Ca^{2+} and Na^+ channels in maintaining normal neuronal excitability and synaptic transmission. However, epilepsy resulting from loss-of-function mutations in *SCN1A* genes encoding voltage-gated Na1.1 channels does occur as haploinsufficiency, as shown in *Scn1a*$^{+/-}$ (Yu et al., 2006) and *Scn1a* mutant knock-in (Ogiwara et al., 2007) mouse models of Dravet syndrome (also called Severe Myoclonic Epilepsy of Infancy). In these mouse models, it is postulated that mutations in $Na_v1.1$ channels selectively impair Na^+ channel function in GABAergic inhibitory interneurons without detectable effects on the excitatory pyramidal neurons, leading to neuronal disinhibition and hyperexcitability. Based on this evidence, one possibility

is that MeHg selectively blocks voltage-gated Ca^{2+} or Na^{+} channels in inhibitory interneurons, but not those in excitatory neurons. Although it is not impossible, no evidence to date has yet shown that MeHg specifically affects Ca^{2+} or Na^{+} channels in inhibitory interneurons and not those in excitatory neurons. The possibility for effects of MeHg on voltage-gated (Kv) and inwardly rectifying (Kir) K^{+} channels contributing to MeHg-induced alterations of seizure susceptibility also appears to be low since these K^{+} channels are generally more resistant to MeHg *in vitro* compared to other voltage-gated ion channels and receptors (Yuan et al., 2005). However, it remains to be determined if this is also the case *in vivo*. Ca^{2+}-activated K^{+} channels, particularly the big and small conductance channels (BK and SK), play an important role in the regulation of neuronal excitability by coupling changes in intracellular Ca^{2+} concentration and membrane potentials, forming afterhyperpolarization and controlling action potential firing pattern (for review, see Vergara et al., 1998; Faber and Sah, 2007; Stocker, 2004; Berkefeld et al., 2010). Similarly, the M-channels of Kv7 (KCNQ) family of K^{+} channels also participate in the regulation of neuronal excitability. Mutations in KCNQ2 and KCNQ3 are associated with benign familial neonatal convulsions (BFNC) (for review, see Cooper and Jan, 2003; Burgess, 2005). However, it remains to be determined whether MeHg actually affects these ion channels in the brain to alter neuronal excitability.

Although glutamate and GABA are the predominant excitatory and inhibitory neurotransmitters, respectively, in the CNS, acetylcholine (ACh) is also an important neurotransmitter that participates in the regulation of neuronal excitability and is critical for learning and memory (for review, see Gold, 2003; Hasselmo, 2006). Activation of ACh receptors (AChRs), particularly muscarinic AChRs (mAChRs), can be excitatory or inhibitory depending on the subtypes of AChRs, and the layers and regions of the cerebral cortex (Haj-Dahmane and Andrade, 1996; Gulledge and Stuart, 2005; Eggermann and Feldmeyer, 2009; Gulledge et al., 2009). Mutations in the α4-subunit gene (CHRNA4) or the β-subunit of the neuronal nicotinic acetylcholine receptor (nAChR) are associated with autosomal dominant nocturnal frontal lobe epilepsy (ADNFLE), a focal syndrome characterized by nocturnal motor seizures (for review, see Lerche et al., 2001; Graves, 2006). MeHg has the potential to affect both nicotinic (Shamoo et al., 1976; Eldefrawi et al., 1977) and muscarinic receptors (Abd-Elfattah and Shamoo, 1981; Castoldi et al., 1996; Coccini et al., 2000; Limke et al., 2004a; Roda et al., 2008). However, whether these effects of MeHg on nicotinic or muscarinic receptors lead to increased or decreased excitability remains to be determined.

Normal neuronal excitability in the brain depends on the well-regulated balance between glutamatergic excitation and GABAergic inhibition. Loss or reduction of GABAergic inhibition leading to hyperexcitability has long been considered to be an important mechanism underlying seizures or epileptogenesis. Mutations in $GABA_A$ receptors are associated with genetic epilepsies (for review, see Benarroch, 2007; Macdonald et al., 2010). MeHg has been shown to inhibit $GABA_A$ receptor-mediated currents (Arakawa et al., 1991; Yuan and Atchison, 2003; Herden et al., 2008), to modulate the benzodiazepine binding site of $GABA_A$ receptors (Komulainen et al., 1995; Fonfría et al., 2001), to cause down-regulation of mRNA levels of $GABA_A$ receptors in cerebellar granule cell cultures (Hogberg et al., 2010) and to disrupt GABAergic signaling in the brain of captive minks (Basu et al., 2010). Most importantly, MeHg appears to preferentially affect inhibitory

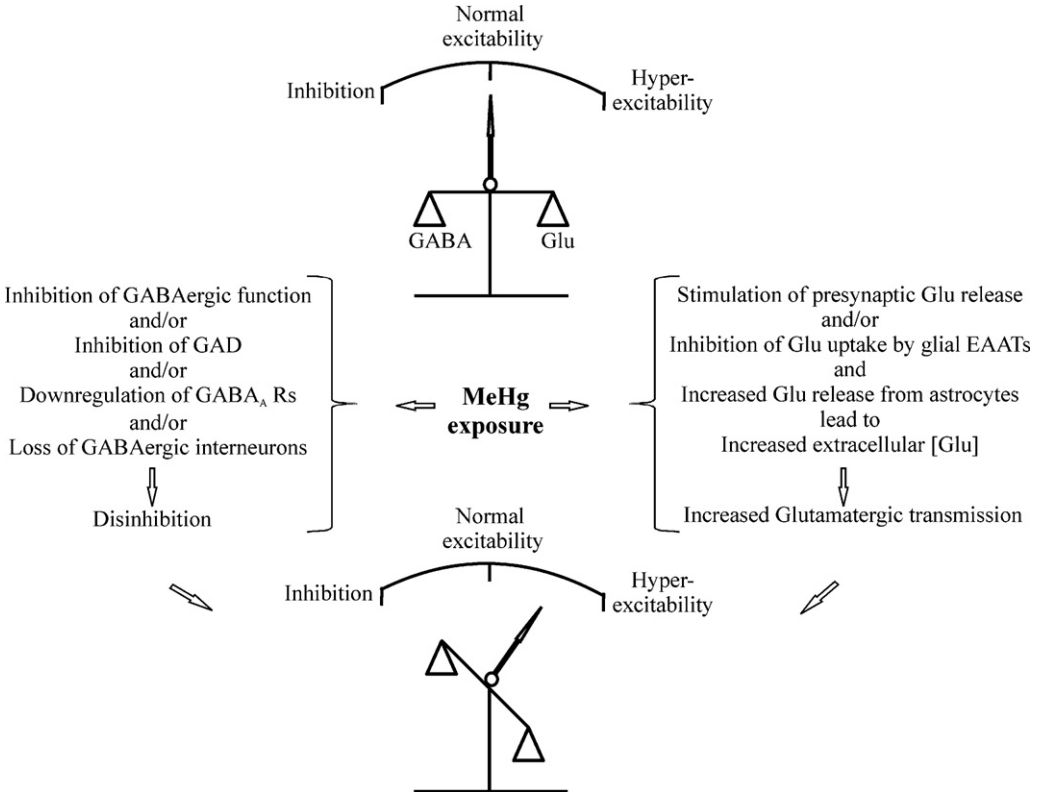

Fig. 1. Schematic diagram of a potential mechanism underlying MeHg-induced changes in neuronal excitability. Under normal conditions, neuronal excitability in the mammalian brains is maintained by well-balanced glutamatergic excitatory and GABAergic inhibitory synaptic activities (Top). Following MeHg exposure, on one hand, MeHg preferentially affects GABAergic inhibitory function result in disinhibition of glutamatergic excitatory function, leading to increased release of neurotransmitter from presynaptic terminals. On the other hand, MeHg also directly stimulates release of glutamate from presynaptic terminals, selectively inhibits glutamate uptake by astrocytes and stimulates glial release of glutamate. These actions will result in an increased extracellular glutamate concentration. Thus, the consequence of the combined effects of MeHg on GABAergic and glutamatergic systems will lead to unbalanced neuronal excitability toward to hyperexcitability direction (Bottom). GABA, gamma-amino butyric acid; Glu, glutamate; GAD, glutamic acid decarboxylase; EAAT, excitatory amino acid transporters.

GABAergic systems over excitatory glutamatergic systems because: (1) the GABAergic interneurons in the neocortex of rats were preferentially impaired following early postnatal MeHg exposure (O'Kusky, 1985). Consistent with this was that the activity of glutamic acid decarboxylase (GAD), a marker for GABAergic neurons, was specifically reduced in the neocortex (O'Kusky and McGeer, 1985; O'Kusky et al., 1988), suggesting a selective loss of GABAergic neurons and terminals. (2) GABAergic inhibitory synaptic transmission appears to be more sensitive to MeHg than is glutamatergic excitatory synaptic transmission in hippocampal slices (Yuan and Atchison, 1995, 1997; Fountain and Rowan, 2000). Similar phenomenon has been observed consistently in experiments in which both GABAergic and glutamatergic responses could be recorded in a given neuron simultaneously: the effects of MeHg on GABAergic responses consistently occured prior to those of MeHg on glutamatergic responses (unpublished observations). (3) Early postnatal exposure of rats to MeHg increased the sensitivity of cortical neurons to $GABA_A$ receptor antagonists and reduced the threshold for glutamatergic excitation (Dasari and Yuan, 2010). Thus, MeHg-induced preferential impairment of GABAergic inhibitory function could lead to hyperexcitability and increased seizure susceptibility.

On the other hand, a direct stimulatory effect of MeHg on glutamatergic function could also contribute to increased susceptibility to seizures. In fact, inhibition by MeHg of glutamate uptake by excitatory amino acid transporters (EAATs) in astrocytes, leading to an increase in extracellular glutamate levels, has been thought to play an important role in MeHg-induced increase in neuronal excitability (Albrecht et al., 1993; Aschner et al., 2000; Juárez et al., 2002). In addition, *in vitro* studies have consistently shown that MeHg always initially stimulates glutamatergic synaptic transmission including increased spontaneous release of glutamate (Yuan and Atchison, 1993, 1995, 1997, 2007; Fountain and Rowan, 2000). However, it appears that this initial stimulatory action is likely a secondary effect, at least in part, resulting from a preferential effect of MeHg on GABAergic function (Yuan and Atchison, 1995, 1997; Fountain and Rowan, 2000). Thus, a preferential effect of MeHg on GABAergic inhibitory system, leading to disinhibition of glutamatergic signaling, is predicted to be, at least partly, responsible for MeHg-induced increases in the susceptibility of mammalian brains, particularly developing brains, to seizures or epilepsy (Fig. 1).

At high level exposure, however, MeHg is known to induce severe brain damage including a gross loss of neurons following neuronal degeneration and death, particularly the layer IV neurons in the neocortex of humans (Hunter and Russell, 1954; Takeuchi et al., 1959, 1962; Nierenberg et al., 1998) and experimental animals (Chang and Hartmann, 1972; Shaw et al., 1975; Syversen et al., 1981; Merigan et al., 1983; O'Kusky, 1985; Wakabayshi et al., 1995; Nagashima et al., 1996; Nagashima, 1997; Eto et al., 2001a, 2001b, 2002). Therefore, it is possible that MeHg-induced neuron loss may result in reactive gliosis and/or neuronal network rewiring and forming aberrant recurrent excitatory circuits similar to those seen in chronic epilepsy resulting from brain trauma, ischemia, tumors, infection and status epilepticus (SE) in humans (for review see Parent and Murphy, 2008; Scharfman and McCloskey, 2009) and subsequently lead to hyperexcitability.

5. Conclusions

The importance of gene–environment interactions in epileptogenesis has been well recognized. However, what and how the environmental factors interact with genetic and other intrinsic factors to alter the susceptibility of humans and animals to epileptic seizures remain poorly understood. In terms of the roles of environmental chemicals in epileptogenesis, our knowledge is even more limited due to the lack of systematic study in this important area.

Epidemiological and animal studies have provided strong evidence that MeHg, a ubiquitous environmental contaminant, is an important risk factor contributing to epileptogenesis. Clearly, acute or chronic exposure to high levels of MeHg induces convulsive seizures. In addition, developmental exposure to relatively low levels of MeHg facilitates seizure induction in animals by other convulsive factors. Although the exact underlying mechanisms remain unclear, a preferential effect of MeHg on GABAergic functions is predicted to contribute to the etiology of epileptogenesis. However, it remains to be determined whether chronic exposure to low levels of MeHg through fish consumption also affects the susceptibility of the human brain, particular the developing brain, to seizure disorders. The latter is particularly important because: (1) the developing brain is highly sensitive to seizure, with seizures occurring more frequently in the neonatal period and early childhood than at any other stages in life (Ronen et al., 1999; Jensen, 2009). (2) Coincidently, the developing brain is also highly sensitive to MeHg (Weiss, 2000; Myers et al., 2009).

Chronic exposure to low levels of certain environmental factors may not directly induce a disease or neurological disorder. However, chronic exposure to these factors may act as risk modifiers to alter the susceptibility and to accelerate the onset of a disease or disorder caused by other pathogens or genetic defects (for review, see Sorg and Prasad, 1997; Bell et al., 1997a, 1997b; Gilbert, 2001). In some cases, effects of early developmental environmental exposure may not be expressed until later in adult life (Vathy, 2001; Landrigan et al., 2005; Doherty et al., 2009; Montandon et al., 2009; Fox et al., 2010). For instance, prenatal methamphetamine or morphine exposure affects the susceptibility of adult rats to convulsive agent-induced seizures (Vathy, 2001; Šlamberová et al., 2008). Prenatal exposure to cigarette smoke affects offspring weight gain and increases risk of developing cardiovascular diseases later in life (Ng et al., 2009). Prenatal coexposure of mercury vapor and MeHg causes interactive behavioral changes in adult rats (Fredriksson et al., 1996). Developmental MeHg exposure alters behavioral and/or neurochemical sensitivity of animals to d-amphetamine and pentobarbital (Rasmussen and Newland, 2001) or amphetamine (Wagner et al., 2007) later in life. Under these circumstances, the contribution of environmental risk factors to the etiology of a neurological disorder is often ignored. This may be especially true for chemicals like MeHg that have a characteristic "latent" period before onset of its toxic effects (Rice and Gilbert, 1982; Harada, 1995; Nierenberg et al., 1998; Weiss et al., 2002). To date, however, no specific epidemiological evidence is available to support an effect of MeHg, particularly at low level MeHg exposure through the consumption of fish and seafood, on seizure susceptibility. Thus, questions remain: (1) Does exposure to low levels of MeHg from fish consumption alter the susceptibility of humans to seizures induced by other intrinsic and extrinsic factors such as gene mutations, fever, audiogenic or chemical convulsive inducers? (2) Is the prevalence rate of neonatal or childhood seizures or epilepsy in populations with long-term consumption of MeHg-contaminated fish or seafood diet higher than that in populations with low fish diet? Interestingly, the prevalence rate (8–14%) of febrile seizures in some regions of Japan and Guam (Mathai et al., 1968; Stanhope et al., 1972; Tsuboi and Okada, 1984; Tsuboi, 1988; Hauser, 1994) are significantly higher than the average worldwide (3–5%). Is this increased incidence rate of febrile seizures related to chronic exposure to MeHg? (3) Does early developmental exposure to MeHg affect the epileptic seizure susceptibility in adulthood? Thus, further investigation of the role of MeHg–gene interactions in alterations of seizure susceptibility is necessary. The outcomes will be helpful for better understanding of the etiology of epilepsy.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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