EJN European Journal of Neuroscience

FENS Federation of European Neuroscience Societies

European Journal of Neuroscience, pp. 1–19, 2015 doi:10.1111/ejn.13028

REVIEW
Prenatal exposure to common environmental factors affects brain lipids and increases risk of developing autism spectrum disorders

Christine T. Wong,[1,2] Joshua Wais[1] and Dorota A. Crawford[1,2,3]
[1]School of Kinesiology and Health Science, York University, Toronto, ON, Canada M3J 1P3
[2]Neuroscience Graduate Diploma Program, York University, Toronto, ON, Canada M3J 1P3
[3]Department of Biology, York University, Toronto, ON, Canada M3J 1P3

Keywords: autism, blood brain barrier, chemicals, lipids, prostaglandin

Edited by Sophie Molholm
Received 29 April 2015, revised 21 July 2015, accepted 23 July 2015

Abstract

The prevalence of autism spectrum disorders (ASDs) has been on the rise over recent years. The presence of diverse subsets of candidate genes in each individual with an ASD and the vast variability of phenotypical differences suggest that the interference of an exogenous environmental component may greatly contribute to the development of ASDs. The lipid mediator prostaglandin E2 (PGE_2) is released from phospholipids of cell membranes, and is important in brain development and function; PGE_2 is involved in differentiation, synaptic plasticity and calcium regulation. The previous review already described extrinsic factors, including deficient dietary supplementation, and exposure to oxidative stress, infections and inflammation that can disrupt signaling of the PGE_2 pathway and contribute to ASDs. In this review, the structure and establishment of two key protective barriers for the brain during early development are described: the blood–brain barrier; and the placental barrier. Then, the first comprehensive summary of other environmental factors, such as exposure to chemicals in air pollution, pesticides and consumer products, which can also disturb PGE_2 signaling and increase the risk for developing ASDs is provided. Also, how these exogenous agents are capable of crossing the protective barriers of the brain during critical developmental periods when barrier components are still being formed is described. This review underlines the importance of avoiding or limiting exposure to these factors during vulnerable periods in development.

Introduction

Autism is a neurodevelopmental disorder defined by impairments in communication, social interactions and language, and is associated with repetitive behaviors (Pelphrey *et al.*, 2014). Autism belongs to a spectrum known as autism spectrum disorders (ASDs), which also includes Asperger's syndrome, childhood disintegrative disorder, and pervasive developmental disorder not otherwise specified. Over recent years, there has been a dramatic increase in the prevalence of ASDs in children. The Centers for Disease Control and Prevention reported that one in 88 children had an ASD in 2008 (CDC, 2012), and in 2010 the prevalence increased to one in 68 children (CDC, 2014). Furthermore, school-aged boys were more than four times as likely to have an ASD compared with their female counterparts (Blumberg *et al.*, 2013). Although some argue that the increased prevalence is the result of changes in diagnostic criteria, this cannot fully explain the observed increases (Hertz-Picciotto & Delwiche, 2009). It is well established that the etiology of ASDs involves the interaction of genetic composition and exposure to environmental factors (Muhle *et al.*, 2004; Herbert, 2010; Meek *et al.*, 2013; Banerjee *et al.*, 2014; Hall & Kelley, 2014; Rossignol *et al.*, 2014; Tordjman *et al.*, 2014; Kim & Leventhal, 2015). Because genes do not evolve very rapidly in evolution, influence of environmental factors might contribute to the developmental differences in ASDs through modifications in gene expression.

There is sufficient research from twin and family studies demonstrating the involvement of genes in ASDs (Guo *et al.*, 2011; Frazier *et al.*, 2014). However, the most recent evidence suggests that in monozygotic twins (MTs) that share the same genetic material, the concordance rates range from 43 to 88% (Rosenberg *et al.*, 2009; Lichtenstein *et al.*, 2010; Stilp *et al.*, 2010; Hallmayer *et al.*, 2011; Ronald & Hoekstra, 2014). Additionally, MTs that are diagnosed with ASDs often display different subsets of autism symptoms (Kates *et al.*, 1998, 2004; Belmonte & Carper, 2006; Mitchell *et al.*, 2009). Furthermore, the concordance rates for dizygotic twins are about double that of non-twin siblings, suggesting that the uterine and maternal environment likely contribute to autism concordance rates (Bohm *et al.*, 2013). This suggests that investigations beyond heritable genetic differences should be taken to uncover the etiologies of ASDs. Various studies on ASDs using animal models and human samples have shown significant differences in gene expression during pre- and postnatal brain development (Garbett

Correspondence: Dr D. A. Crawford, [1]School of Kinesiology and Health Science, as above.
E-mail: dakc@yorku.ca

et al., 2008; Bhogal *et al.*, 2013; Gupta *et al.*, 2014). Gene expression studies in individuals with ASDs have revealed dysregulation of particular pathways, including those involved with the immune response, cell communication and motility, and neuronal differentiation (Garbett *et al.*, 2008; Gupta *et al.*, 2014). Given that the expression of genes as a result of gene–environment interactions determines phenotype outcomes (Kanherkar *et al.*, 2014), exposure to environmental risk factors during vulnerable developmental periods may alter gene expression and contribute to the phenotypes of ASDs.

The development of the human brain and nervous system is extraordinarily complex, involving time-sensitive events that are impacted by an ongoing interplay of genetic and environmental factors. Human brain development begins in the 3rd week of gestation and continues after birth through to adolescence, and arguably into adulthood (Stiles & Jernigan, 2010). Normal prenatal development of the brain (including events like cell fate specification and axon guidance) requires highly specific signaling from key biological pathways (Charron & Tessier-Lavigne, 2005). These pathways carefully regulate the expression of genes, which can be turned on or off during different stages of development and expressed in specific concentration gradients (Charron & Tessier-Lavigne, 2005). The environment, endogenous signals found within the brain and exogenous agents originating outside the body, can influence gene expression during development (Andersen, 2003). Exposure to exogenous insults can perturb the normal developmental trajectory during the critical prenatal and perinatal period (Andersen, 2003). The foundations for brain formation are being established during this period, making it particularly susceptible to harmful environmental agents that may occur through maternal exposure (Moore & Persaud, 1998; Tannahill *et al.*, 2005). In order for exogenous agents to affect the developing embryo or fetus, they must pass through protective barriers, the blood–brain barrier (BBB) in the fetus and the placental barrier. Both barriers develop during early pregnancy and act as a maternal–fetal filter to regulate the flow of specific nutrients and substances (Ballabh *et al.*, 2004; Syme *et al.*, 2004; Saunders *et al.*, 2012). Knowing what substances are capable of passing through these barriers is crucial in determining potential risks for the developing brain.

Because the human brain contains high lipid content, healthy development of the brain relies on the supply and function of these macromolecules (Calderon & Kim, 2004). Fatty acids are the simplest form of lipids that serve as the building blocks for more complex lipids, such as phospholipids, cholesterol and vitamin E. A sufficient supply and balance of fatty acids is integral to cell membrane integrity, which is an indicator for healthy development, maintenance and function of the nervous system (Lawrence, 2010). Environmental factors such as diet, increased levels of oxidative stress, and exposure to infections and inflammation can lead to altered lipid metabolism (Adibhatla & Hatcher, 2008; Tamiji & Crawford, 2010a,b; Wong & Crawford, 2014).

Lipid mediators such as prostaglandin E2 (PGE_2) are key molecules important in the development and function of the human brain (Uauy & Dangour, 2006; Innis, 2007; Carlson, 2009). PGE_2 is one of the major lipid metabolites released from phospholipid membranes through the action of phospholipase A2 and cyclooxygenase (COX) enzyme activity. PGE_2 is important in various brain functions, including the masculinization of the brain and behavior (Amateau & McCarthy, 2004; Lenz *et al.*, 2013), dendritic spine formation (Amateau & McCarthy, 2002), synaptic plasticity (Koch *et al.*, 2010), calcium regulation in growth cones (Tamiji & Crawford 2010b), and the survival, proliferation, migration and differentiation of neural stem cells (Jiang *et al.*, 2010). Moreover, it is capable of modifying the signaling of crucial developmental pathways, including the Wnt signaling pathway (Buchanan & DuBois, 2006; Evans, 2009; Goessling *et al.*, 2009; Wong *et al.*, 2014).

It has previously been described that abnormal PGE_2 signaling [which can result from genetic defects or exposure to environmental factors, including deficient dietary supplementation, increased exposure to drugs (i.e. prostaglandin E analog, misoprostol), oxidative stress, infections and inflammation] has been highly implicated in the etiology of ASDs (Tamiji & Crawford, 2010a,b; Wong & Crawford, 2014). This review provides a unique summary of additional common environmental risk factors capable of directly or indirectly disrupting PGE_2 signaling, such as air pollutants, compounds found in food products and personal care products like cosmetics. It is discussed how these compounds cross the key protective barriers (BBB and placental barrier) during critical periods of early brain development, and how they may contribute to the development of ASDs. An overview of developmental timelines for the structural components of the BBB and placental barrier for the developing brain is also given.

Protective barriers

During prenatal development, protective mechanisms act as interfaces between the brain and the environment. Two main protective barriers are the BBB and the placental barrier. The BBB is an essential physiological barrier that controls and restricts the movement of materials between the blood and the CNS in the fetus. Some functions of the BBB include ion regulation, control of neurotransmitter concentrations, macromolecule entry and exit, neurotoxin levels, and overall brain nutrition (Abbott *et al.*, 2010). The placenta is an integral organ for the developing embryo and fetus. Its role involves transfer of nutrients and respiratory gases from the mother to the fetus, removal of metabolic waste products from the fetus to the mother, and synthesis of steroids, hormones and peptides that are necessary for the successful progression of pregnancy (Syme *et al.*, 2004; Behravan & Piquette-Miller, 2007; Aye & Keelan, 2013). Similar to the BBB, the placental barrier has a role as a selective filter for potential harmful substances circulating in the maternal blood (Syme *et al.*, 2004; Bhattacharjee *et al*., 2012). The mechanisms by which various substances are transported into the fetal CNS across protective barriers and their developmental timeline is crucial in understanding the potential impact of various environmental agents on early development and identifying the developmental periods of vulnerability, respectively.

The structure and development of the BBB

The complex protective mechanisms of the BBB are acquired over the course of development in cells that build its structure, including cerebral microvasculature endothelial cells, pericytes, astrocytes and microglia. Moreover, the basement membrane, a thin sheet that surrounds all cerebral microvasculature, acts as an integral part of the BBB by connecting these various cells (Ballabh *et al.*, 2004). Together these components comprise the 'neurovascular unit', which is crucial for determining what nutrients and molecules can enter the brain during early development (Abbott *et al.*, 2006, 2010; Fig. 1). The developmental emergence of these components is also described below (Fig. 2).

Cerebral capillary endothelial cells are arranged in a thin and continuous layer in order to form the BBB (Fig. 1). Endothelial cells in the BBB are unique from those found in the rest of the body.

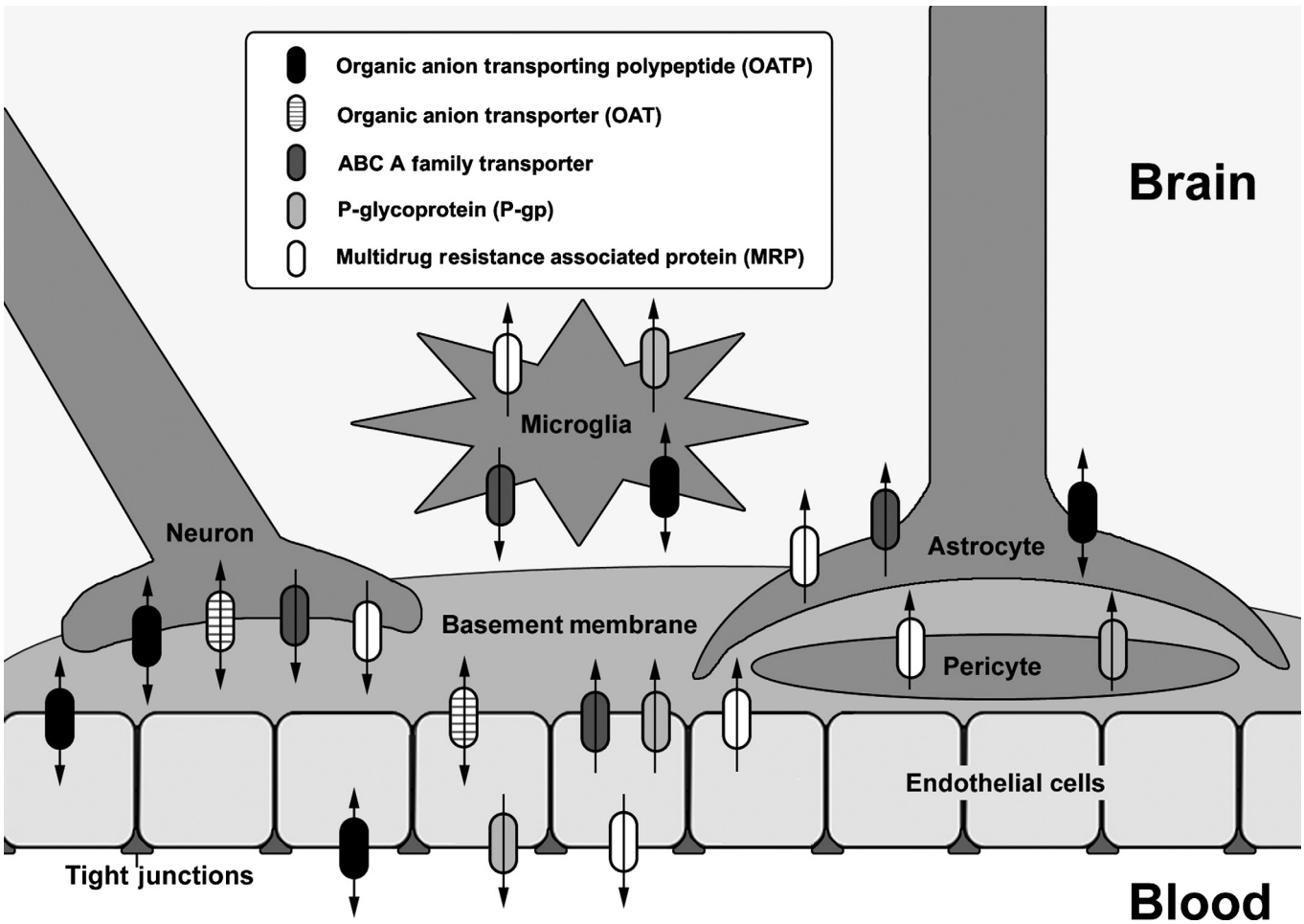

FIG. 1. The BBB is composed of brain endothelial cells, astrocytes, pericytes, microglia and the basement membrane. Altogether, these components make up the 'neurovascular unit', which is important for regulating the passage of nutrients and molecules in and out of the brain that will impact the function and activity of neurons during development.

Firstly, there is an abundance of apical tight junctions (TJs) between adjacent cerebral endothelial cells (de Vries *et al.*, 1997; Ek *et al.*, 2012). These TJs serve to fuse cerebral endothelial cells together, significantly reducing the trafficking of substances (like ions and polar solutes) between the blood and the CNS. Moreover, cerebral endothelial cells have high densities of cytosolic mitochondria (de Vries *et al.*, 1997) due to energy-dependent transport of molecules across the BBB that requires adenosine triphosphate (ATP). Furthermore, pinocytotic endocytosis is minimal in cerebral endothelial cells, implying that fluid uptake is limited (Cervos-Navarro *et al.*, 1988). Cerebral endothelial cells are capable of restricting the diffusion of large and hydrophilic molecules into the brain's extracellular fluid. They contain numerous unidirectional and bidirectional transporters that move required materials, such as water, glucose, fatty acids and amino acids through carrier-mediated transport. However, small hydrophobic or lipophilic molecules may travel along a concentration gradient. The differentiation of endothelial cells, also known as vasculogenesis, occurs at approximately gestational week 8 in human embryos (Volpe, 1995; Fig. 2). Angiogenesis, the process of creating new blood vessels, first occurs in the nervous system at about 12 weeks gestation in humans (Volpe, 1995) and embryonic day (E)10 in mice (Bauer *et al.*, 1993; Daneman *et al.*, 2009). The TJs that exist between cerebral endothelial cells have been reported to be formed immediately as blood vessels invade neural tissues at E10 in mice, E11 in rats, and between 8 and 12 weeks of gestation in humans (Mollgard & Saunders, 1975; Saunders *et al.*, 2000). TJs continue development until birth (Kniesel *et al.*, 1996; Anstrom *et al.*, 2007) and may increase in complexity with age, thus providing further restrictive control across the BBB after birth (Schulze & Firth, 1992).

Pericytes are critical in the maintenance and maturation of the BBB (Fig. 1; Armulik *et al.*, 2010). They are contractile cells that support the integrity of the BBB by surrounding the brain capillaries and providing structural support (Daneman *et al.*, 2010b). They play a role in controlling vascular permeability, regulating rate of transcytosis and in preventing the influx of immune cells into the CNS (Daneman *et al.*, 2010b). Additionally, pericytes are capable of phagocytosis (Fisher, 2009). It has been determined that pericytes proliferate during angiogenesis in the CNS; however, the development of pericytes, including its proliferation, migration and differentiation, is still not well characterized in humans (Armulik *et al.*, 2011). In the mouse brain, pericytes accompany newly differentiated cerebral endothelial cells at E10 (Fig. 2; Bauer *et al.*, 1993).

Two types of glia, astrocytes and microglia, are members of the neurovascular unit (Fig. 1). Astrocytes are attached to the basement membrane and surround the microvasculature of the brain (Ballabh *et al.*, 2004). They are important for expressing multiple transporter proteins – both on the astrocytes themselves and on neighboring

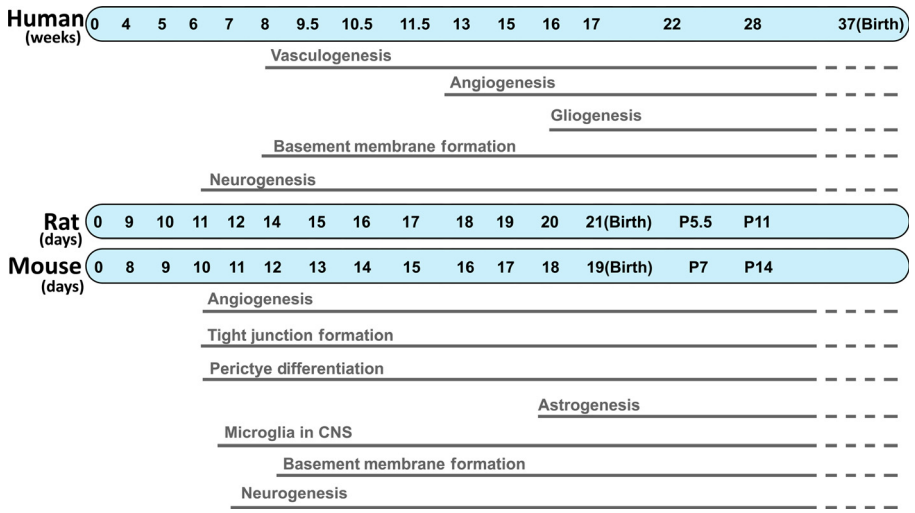

FIG. 2. The timelines of key developmental processes in the BBB in the human and rodent models is depicted. Processes include vasculogenesis, angiogenesis, TJ formation, pericyte differentiation, gliogenesis, basement membrane formation and neurogenesis.

endothelium and neurons (Decleves *et al.*, 2000; Berezowski *et al.*, 2004). Astrocyte-derived factors, such as sonic hedgehog (Shh; Alvarez *et al.*, 2011), angiotensinogen (Wosik *et al.*, 2007) and retinoic acid (Mizee *et al.*, 2013), have been shown to play roles in the maintenance and modulation of the expression and polarization of transporter proteins in the BBB (Abbott, 2002; Banerjee & Bhat, 2007). In addition, glutamate-mediated calcium concentrations in astrocytes can modify neural activity and vasodilation (Zonta *et al.*, 2003). Microglial cells are the most abundant innate immune cell in the CNS (da Fonseca *et al.*, 2014). Activated microglia can synthesize different chemicals, including free radicals, lipid mediators (e.g. prostaglandins), proinflammatory cytokines and chemokines (Perry *et al.*, 2010). Moreover, microglia play a role in CNS angiogenesis, and mediate the stabilization and fusion of cerebral endothelial cells (da Fonseca *et al.*, 2014). Gliogenesis begins at about 16 weeks of gestation in humans (Fig. 2; Holden, 2008). Astrogenesis begins at about E18 and continues postnatally in the rodent CNS (Sauvageot & Stiles, 2002; Tien *et al.*, 2012). Microglia originate in the yolk sac outside of the embryo and migrate into the mouse CNS as early as E10.5, where they continue to mature postnatally (Nayak *et al.*, 2014).

The non-cellular component of the BBB is the basement membrane (Fig. 1), which is mainly composed of type IV collagen, fibronectin and laminin, and completely covers the cerebral endothelial cells (Hawkins *et al.*, 2006). Pericytes are embedded into the basement and astrocyte processes surround the basement membrane (Hawkins *et al.*, 2006). The basement membrane is an essential component to the neurovascular unit because it regulates intercellular crosstalk (Obermeier *et al.*, 2013). Altogether, the basement membrane and adjacent cells help maintain the structure and function of the BBB. Initial formation of the basement membrane begins at about 8 weeks of gestation in the human (Roediger *et al.*, 2010) while, in the rodent model, the basement membrane first appears at E14 in the rat, and its main period of thickening is from the 3rd to 4th postnatal weeks (Fig. 2; Bar & Wolff, 1972; Stewart & Hayakawa, 1987).

The BBB acts as a barrier to protect the development and function of neurons. Neurons are also important in the induction and formation of the BBB (Banerjee & Bhat, 2007). Signal transmission between neurons, glial cells and endothelial cells of the BBB contribute to its function (Fig. 1; Banerjee & Bhat, 2007). In the developing human brain, neurogenesis precedes gliogenesis and begins in the embryonic period at about 6 weeks gestation (Fig. 2; Stiles & Jernigan, 2010). By 14 weeks gestation, human neurogenesis peaks and is largely complete by 25 weeks gestation (Holden, 2008). In comparison, neurogenesis occurs between E11 and E17 in the developing mouse brain, and between E11 and E21 in the developing rat brain (Jacobson, 1991).

The structure and development of the placental barrier

Fetal tissue can come into direct contact with maternal blood through the placenta. The placenta has key roles in the transport of nutrients and waste products (Brett *et al.*, 2014). Similarly to the BBB, it can act as a selective barrier to protect the fetus from endogenous and exogenous toxins (Aye & Keelan, 2013). The primary barrier of the placenta that separates the maternal and fetal blood is the continuous layer of syncytiotrophoblast cells (otherwise known as the placental epithelium; Bloxam *et al.*, 1997). The human placenta contains about 15–40 functional vascular compartments known as cotyledons (Syme *et al.*, 2004; Aye & Keelan, 2013). Each cotyledon is made up of fetal tissue organized into villous tree-like structures. These tree-like structures have a central capillary for the fetus and an outer trophoblast layer (comprised of syncytiotrophoblast cells), which is surrounded by maternal blood (Syme *et al.*, 2004; Aye & Keelan, 2013). Both uptake and efflux transporters can be found at the apical and basal membranes of the syncytiotrophoblasts (Evseenko *et al.*, 2006; Vahakangas & Myllynen, 2009). Arteries connecting the placenta and the maternal circulation via the uterus are present from the 4th gestational week in humans; however, it is not until the 8–10th week of gestation in humans that these arteries become functional and allow maternal blood flow through the placenta (Burton *et al.*, 1999; Syme *et al.*, 2004). Between the 10th and 38th week of gestation, the blood flow through the placenta from the mother increases significantly (Aye & Keelan, 2013), which indicates that during this period of vulnerability, there is an increased risk for the fetus to be exposed to potentially harmful substances that may be present in the mother's circulation.

Transport systems across protective barriers

In addition to the physical barrier of the BBB and the placenta described above, transport systems are in place to regulate the passage of different exogenous and endogenous compounds (Figs 1 and 3). These transport systems include protein transporters that

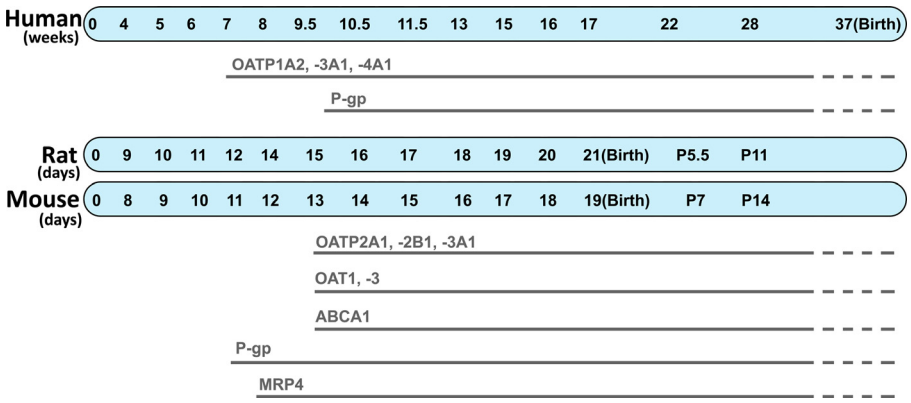

FIG. 3. The timelines for the emergence of relevant transport systems in the BBB in human and rodent models is illustrated. OATP, OAT, ABCA, P-gp and MRP transporters can all affect the movement to and from the BBB of signaling molecules in the PGE2 lipid pathway. Some of these transporters that normally shuttle endogenous compounds and nutrients have also been shown to transport exogenous drugs, toxins, estrogen-mimicking chemicals and pesticides that could be harmful to the developing nervous system.

enable specificity for nutrients necessary for normal brain development and function (Table 1). However, the emergence of these transporters during development also provides a means for fetal exposure to environmental agents. Thus, these transport systems are crucial in brain development but may also introduce vulnerability to particular substances.

Various transport systems are present in the BBB and placenta, including passive diffusion and protein-mediated transport. Passive diffusion can allow lipid-soluble substances to spontaneously cross the membrane along a concentration gradient without the expenditure of cellular energy. However, large and hydrophilic molecules require protein-mediated transport that utilizes energy. Fatty acids have been shown to move across membranes through both diffusion and specific protein-mediated transport (Hamilton *et al.*, 2001; Schwenk *et al.*, 2010). Protein-mediated transport of PGE_2 signaling molecules includes solute-linked carrier (SLC) and ATP-binding cassette (ABC) proteins. Transporters belonging to the SLC class are involved in both uptake and efflux transport of substances in the CNS, and those important for PGE_2 transport include organic anion transporting polypeptides (OATPs) and organic anion transporters (OATs). Conversely, transporters belonging to the ABC transporter family are the main efflux transporters of both endogenous and exogenous molecules (Girardin, 2006), and those from the ABC A and ABC C family can regulate the transport of PGE_2 and relevant molecules from its pathway. The net transport of a specific compound or drug relies on the interplay between multiple transporters and transport systems, which can work in parallel or opposing directions.

OATPs/SLCO

OATPs are members of the SLCO family (Meier-Abt *et al.*, 2005) and accommodate the transport of a broader substrate specificity, often transporting large organic anions, opioid peptides, thyroid hormones and a wide range of pharmaceutical drugs (Roth *et al.*, 2012; Hagenbuch & Stieger, 2013). These transporters act as anion exchangers – capable of exchanging a drug or exogenous substance for another ion or an endogenous molecule, in a sodium-independent manner (Hagenbuch & Meier, 2004). Five different OATPs that are capable of transporting PGE_2 have been found at various levels of the BBB (Fig. 1; Table 1): OATP1A2; OATP2A1; OATP2B1; OATP3A1; and OATP4A1 (Reichel *et al.*, 1999; Tamai *et al.*, 2000; Bronger *et al.*, 2005; Huber *et al.*, 2007; Scafidi *et al.*, 2007; Choi *et al.*, 2008; Roberts *et al.*, 2008; Chan *et al.*, 2011; Hagenbuch & Stieger, 2013). These specific OATPs are also present in the placental barrier between the mother and fetus (St-Pierre *et al.*, 2002; Briz *et al.*, 2003; Ugele *et al.*, 2003; Aleksunes *et al.*, 2008; Loubiere *et al.*, 2010; Hagenbuch & Stieger, 2013). In addition to PGE_2, these transporters have been shown to transport substrates such as other prostaglandin metabolites and estrogen compounds (Lee *et al.*, 2001; Loscher & Potschka, 2005; Taogoshi *et al.*, 2005; Grube *et al.*, 2006; Vahakangas & Myllynen, 2009; Chan *et al.*, 2011; Roth *et al.*, 2012; Hagenbuch & Stieger, 2013). A study by Chan and colleagues (Chan *et al.*, 2011) found that OATPs were present in the human fetal cerebral cortex by 7–9 weeks gestation (Fig. 3). A recent study by Krazter and colleagues (Kratzer *et al.*, 2013) examined developmental brain tissue from rat, and found that OATPs first appeared on E15 and peaked in expression between E15 and postnatal day 2 (P2).

Of all of the OATPs found at various areas of the BBB, OATP2A1 (also known as prostaglandin-transporter or PGT) is of particular interest. It is largely important in the transport of eicosanoids and various prostaglandins to and from the CNS. PGT was found to be expressed most in the cortex, followed by the cerebellum, hippocampus and finally the brainstem (Scafidi *et al.*, 2007); all areas of the brain that have been implicated in ASDs (Hashimoto *et al.*, 1995; Tuchman, 2003). Interestingly, acetylsalicylic acid and other non-steroidal anti-inflammatory drugs (NSAIDs), which are drugs capable of inhibiting the COX enzyme responsible for PGE_2 production, also act as inhibitors for the OATP2A1 transporter (Taogoshi *et al.*, 2005; Roth *et al.*, 2012; Hagenbuch & Stieger, 2013).

OATs/SLC22A

OATs belong to the SLC22A gene family, and have multi-specificity and transport a wide range of endogenous and exogenous compounds, including: PGE_2, $PGF_{2\alpha}$, medium chain fatty acids, statins, diuretics, antibiotics, NSAIDs, and certain toxins such as pesticides (Lee *et al.*, 2001; Alebouyeh *et al.*, 2003; Ugele *et al.*, 2003; Loscher & Potschka, 2005; Klaassen & Aleksunes, 2010; Ek *et al.*, 2012; Tachikawa *et al.*, 2012; Koepsell, 2013). OATs are also capable of bidirectional transport and function without the need of sodium (Rizwan & Burckhardt, 2007; Koepsell, 2013). OAT1 and OAT3 are expressed in the BBB (Pavlova *et al.*, 2000; Alebouyeh *et al.*, 2003; Bahn *et al.*, 2005; Roberts *et al.*, 2008; Kratzer *et al.*,

TABLE 1. Transporters at the BBB affecting the prostaglandin signaling pathway

Transporter	Description	References
Organic anion transporting polypeptides (OATPs)		
OATP1A2 (SLCO1A2/ OATP-A)	Localization: luminal membrane of brain capillary endothelial cells	Geier and Geier (2007), Gabbianelli *et al.* (2009), Geier *et al.* (2009)
	Developmental emergence: 7–9 weeks gestation (human fetal cerebral cortex)	Grandjean and Landrigan (2006)
	Substrates: PGE_2, bile salts, organic anions and cations, cholate, taurocholate, glycocholate, estradiol-17-glucuronide, estrone-3-sulfate, DHEAS, triiodothyonine, thyroxine, statins, unoprostone metabolite, opioid peptides	Hamilton *et al.* (2001), Garbett *et al.* (2008), Evans (2009), Gabbianelli *et al.* (2009), Hallmayer *et al.* (2011)
OATP2A1 [SLCO2A1/ prostaglandin-transporter (PGT)]	Localization: neurons, astrocytes, microglia	Girardin (2006), Goessling *et al.* (2009)
	Developmental emergence: E15 (rat), peak at E19 (rat)	Hawkins *et al.* (2006)
	Substrates: Eicosanoids, PGE_2, PGD_2, PGE_1, PGF_{2a}, thromboxane B2, latanoprost acid, PGH_2	Garbett *et al.* (2008), Gabbianelli *et al.* (2009), Hartz and Bauer (2011)
OATP2B1 (SLCO2B1/ OATP-B)	Localization: abluminal membrane of brain capillary endothelial cells	Geier and Geier (2007), Gabbianelli *et al.* (2009), Goines and Ashwood (2013)
	Developmental emergence: E15 (rat), peak at E15–P2 (rat)	Hawkins *et al.* (2006)
	Substrates: PGE_2, dehydroepiandrosterone, bromosulfophthalein, taurocholate, estrone-3-sulfate, DHEAS, tyroxine, bromosulfophthalein, statins, latanoprost acid, pregnolone sulfate, unoprostone metabolite	Hashimoto *et al.* (1995), Garbett *et al.* (2008), Gabbianelli *et al.* (2009)
OATP3A1	Localization: neuroglial cells of frontal cortex gray matter, neuronal cell bodies & axons	Goldman and Koduru (2000)
	Developmental emergence: 7–9 weeks gestation (human fetal cerebral cortex) E15 (rat), peak at P2 (rat)	Grandjean & Landrigan (2006), Hawkins *et al.* (2006)
	Substrates: PGE_2, PGE_1, PGF_{2a}, arachidonate, estrone-3-sulfate, tyroxine, vasopressin	Grandjean & Landrigan (2006), Garbett *et al.* (2008), Gabbianelli *et al.* (2009)
OATP4A1 (SLCO4A1/ OATP-E)	Localization: neurons	Grandjean & Landrigan (2006), Grube *et al.* (2006), Gabbianelli *et al.* (2009)
	Developmental emergence: 7–9 weeks gestation (human fetal cerebral cortex)	Grandjean & Landrigan (2006)
	Substrates: PGE_2, taurocholate, estradiol-17-glucuronide, estrone-3-sulfate, triiodothyonine, thyroxine, unoprostone metabolite	Grandjean & Landrigan (2006), Garbett *et al.* (2008), Evans (2009), Gabbianelli *et al.* (2009)
Organic anion transporters (OATs)		
OAT1 (SLC22A6)	Localization: neurons	Houlihan *et al.* (2005)
	Developmental emergence: E15 (rat) and E12 (mouse)	Howdeshell *et al.* (2003), Hawkins *et al.* (2006)
	Substrates: PGE_2, PGF_{2a}, medium chain fatty acids, cyclic AMP and GMP, dicarboxylates, a-ketoglutarate, citrulline, urate, hydroxicinnamic acids, statins, i-lactam antibiotics, diuretic drugs, antiviral drugs, H2 receptor antagonists, NSAIDs (acetylsalicylate, ketoprofen, ibuprofen, indomethacin), nephrotoxin	Heudorf *et al.* (2007), Hertz-Picciotto *et al.* (2008), Hertz-Picciotto and Delwiche (2009), Hallmayer *et al.* (2011)

(continued)

Table 1. (continued)

Transporter	Description	References
OAT3 (SLC22A8)	Localization: abluminal membrane of brain capillary endothelial cells	Howdeshell *et al.* (2003), Hawkins *et al.* (2006), Hertz-Picciotto and Delwiche (2009), Goines and Ashwood (2013)
	Developmental emergence: E15 (rat), E14 (mouse), peak at E14–E16 (mouse)	Howdeshell *et al.* (2003), Hawkins *et al.* (2006)
	Substrates: PGE_2, PGF_{2a}, cimetidine, cortisol, cyclic AMP, DHEAS, estrone-3-sulfate, estradiol-17a-glucuronide, statins, taurocholate, cholate, indoxyl sulfate, vanilmandelic acid, urate, antibiotics, antiviral drugs, H2 receptor antagonist drugs, diuretic drugs, antihypertensive drugs, antidiabetic drugs, neuroprotective drugs, NSAIDs (acetylsalicylate, ketoprofen, ibuprofen, indomethacin), toxins (ochratoxin A, perfluorooctanoic acid, aflatoxin B1), pesticides (2,4-D-dichlorophenoxyecetic)	Hamilton *et al.* (2001), Hagenbuch and Meier (2004), Heudorf *et al.* (2007), Hertz-Picciotto *et al.* (2008), Hertz-Picciotto and Delwiche (2009), Hallmayer *et al.* (2011), Heyer *et al.* (2012), CDC (2013)
ABC A family transporters (ABCA-)		
ABCA1	Localization: abluminal membrane of brain capillary endothelial cells, astrocytes, neurons, microglia	Jacobson (1991), Ishido *et al.* (2004), Carlson (2009), Jiang *et al.* (2010)
	Developmental emergence: E13 (mouse)	Innis (2007)
	Substrates: Phospholipids, vitamin E (a-tocophenol), cholesterol and oxysterols, apolipoprotein A1, apolipoprotein E, interleukin-1	Ikezuki *et al.* (2002), Carlson (2009)
ABC B family transporters (ABCB-)/P-glycoprotein (P-gp)		
ABCB1/P-glycoprotein (P-gp)	Localization: luminal and abluminal membrane of brain capillary endothelial cells, microglia, pericytes	Johnson-Restrepo *et al.* (2005), Dallas *et al.* (2006), Carlson (2009), Evans (2009), Jolous-Jamshidi *et al.* (2010), Hallmayer *et al.* (2011)
	Developmental emergence: E10.5 (mouse), E13 (rat), 10–12 weeks gestation (human)	Kang *et al.* (2003), Kalkbrenner *et al.* (2010), Jomova and Valko (2011), Jurewicz *et al.* (2013)
	Substrates: estradiol-17-glucuronide, estrone, ethynyl estradiol, anticancer drugs, protease inhibitors, statins, cardiac-related drugs, tetracycline, cyclosporin, corticosteroids, analgesics, cytokines, histamine receptor antagonists, calcium channel blockers, antidepressants	Hamilton *et al.* (2001), Johnson-Restrepo *et al.* (2005), Hertz-Picciotto *et al.* (2008), Evans (2009), Frazier *et al.* (2014)
ABC C family transporters (ABCC-)/multidrug resistance-associated proteins (MRP-)		
MRP2 (ABCC2)	Localization: luminal membrane of brain capillary endothelial cells	Kates *et al.* (1998), Kates *et al.* (2004), Johnson-Restrepo *et al.* (2005), Evans (2009)
	Developmental emergence: not yet determined	
	Substrates: PGE_2, acetaminophen-glucuronide, acetaminophen-sulfate, glutathione conjugates, taurocholate, leukotrienes, cholate, glycocholate, morphine-3-glucuronide, estradiol-17-glucuronide, HIV protease inhibitors, anticancer drugs	Hamilton *et al.* (2001), Kim *et al.* (2006), Hertz-Picciotto *et al.* (2008), Evans (2009), Jolous-Jamshidi *et al.* (2010)
MRP4 (ABCC4)	Localization: luminal and abluminal membrane of brain capillary endothelial cells, astrocytes, neurons, microglia, pericytes	Kates *et al.* (2004), Johnson-Restrepo *et al.* (2005), Dallas *et al.* (2006), Kaur *et al.* (2007), Kern *et al.* (2007), Kern *et al.* (2010), Kern *et al.* (2011)
	Developmental emergence: E13 (rat)	Jurewicz *et al.* (2013)
	Substrates: PGE_2, PGE_1, PGF_{2a}, cyclic AMP and GMP, DHEAS, estradiol-17-glucuronide, folate, leukotrienes, taurocholate, thromboxane B2, glutathione-, sulfate-, and glucuronate-conjugated drugs, anticancer drugs, anti-HIV drugs, conjugated steroids and bile acids	Hamilton *et al.* (2001), Johnson-Restrepo *et al.* (2005), Kim *et al.* (2006), Huber *et al.* (2007), Hertz-Picciotto *et al.* (2008), Jolous-Jamshidi *et al.* (2010)

2013) and in the placental barrier (Ugele *et al.*, 2003; Evseenko *et al.*, 2006; Koepsell, 2013; Fig. 1). To date, the temporal expression of OAT1 and OAT3 has been established in rodents (Fig. 3). OAT1 expression has been reported as early as E15 (rat) and E12 (mouse), while OAT3 expression was detected at E15 (rat) and E14 (mouse), with peak expression between E14 and E16 in the mouse (Pavlova *et al.*, 2000; Kratzer *et al.*, 2013).

ABC A proteins

Potentially one of the most influential classes of transporters in the efflux of foreign and toxic compounds is the ABC family of efflux transporters. They are transmembrane proteins that obtain their energy through ATP hydrolysis and act as active efflux pumps for a wide range of compounds, often against a concentration gradient (Girardin, 2006; Hartz & Bauer, 2011). ABC transporter proteins are largely responsible for extruding metabolic wastes and limiting the entry of toxins and drugs to the brain (Hartz & Bauer, 2011), and thus are crucial for neuroprotection in the brain.

The ABC A family of transporters has a key role in sterol homeostasis, cholesterol transport, plasma membrane fluidity and lipid metabolism in the brain (Hartz & Bauer, 2011; Tarling *et al.*, 2013). ABCA1 is expressed in the BBB and placental barrier, and has a key role in the ejection of plasma membrane phospholipids and cholesterol (Bhattacharjee *et al.*, 2012; Aye & Keelan, 2013; Fig. 1). Substrates of ABCA1 include cholesterol, phospholipids and vitamin E (Bhattacharjee *et al.,* 2012; Tarling *et al.*, 2013). To date, the evidence shows that ABCA1 is expressed as early as E13 in the BBB, astrocytes, microglia and neurons in the developing mouse brain (Koldamova *et al.*, 2003; Tachikawa *et al.*, 2005; Kim *et al.*, 2006; Fujiyoshi *et al.*, 2007; Fig. 3).

ABC B proteins/P-glycoprotein (P-gp)

Taking into account all members of the ABC transporter families found in the CNS, ABCB1, also called P-gp, has been studied the most (Hartz & Bauer, 2011). P-gp has been regarded as one of the most important components of the brain and placental barriers in preventing the entry of harmful exogenous compounds (Hartz & Bauer, 2011; Tarling *et al.*, 2013). P-gp has a broad substrate specificity, which includes: lipid compounds, various drugs, steroids and cytokines (Kusuhara & Sugiyama, 2005; Loscher & Potschka, 2005; Girardin, 2006; Vahakangas & Myllynen, 2009; Klaassen & Aleksunes, 2010). P-gp is localized in the luminal and abluminal membrane of cerebral endothelial cells, microglia and pericytes (Lee *et al.*, 2001; Berezowski *et al.*, 2004; Kusuhara & Sugiyama, 2005; Dallas *et al.*, 2006; Vahakangas & Myllynen, 2009; Bhattacharjee *et al.*, 2012; Fig. 1). The expression of P-gp has been detected as early as E10.5 in the mouse (Qin & Sato, 1995), E13 in rats (Ek *et al.*, 2010) and 10–12 weeks gestation in the human (Schumacher & Mollgard, 1997; Virgintino *et al.*, 2008; Fig. 3). Notably, the expression of P-gp is much higher in the adult, suggesting that the developing brain may be particularly vulnerable to substrates of P-gp (Daneman *et al.*, 2010a).

ABC C proteins/multidrug resistance-associated proteins (MRPs)

The ABC C family is also known as MRPs. Similar to the other ABC transporters, MRPs function to export molecules out of the cells. MRP2 (ABCC2) and MRP4 (ABCC4) are found in the BBB and placental barrier (Miller *et al.*, 2000; St-Pierre *et al.*, 2000; Zhang *et al.*, 2000, 2004; Dombrowski *et al.*, 2001; Berezowski *et al.*, 2004; Leggas *et al.*, 2004; Nies *et al.*, 2004; Kusuhara & Sugiyama, 2005; Vahakangas & Myllynen, 2009; Aye & Keelan, 2013; Fig. 1). MRP2 or canalicular multispecific OAT functions to efflux glutathione and glucuronide conjugates, organic anions, nucleotide analogs and anti-cancer drugs (Tian *et al*., 2005). MRP4 is involved in the efflux of sulfate- and glucuronide-conjugated steroids, prostaglandins, folate nucleotides, and nucleoside analogs (Loscher & Potschka, 2005; Klaassen & Aleksunes, 2010). During development, MRP4 is expressed in the rodent BBB as early as E13 and increases through adulthood (Ek *et al.*, 2010; Fig. 3).

Development of barriers and vulnerability to chemical exposure

Altogether, the development of the BBB and placental barrier commences around the 7th week of gestation in humans, and continues throughout prenatal development. Given that blood flow from the mother across the placenta does not occur until the 8–10th week of gestation, increased vulnerability of exposure to environmental risk factors for the developing fetus may occur following this time period. Rodent studies mirror the developmental timelines in human studies and provide additional developmental information on the emergence of particular transporters for chemicals that have yet been studied in humans. This review describes for the first time the possible mechanisms by which the PGE_2 signaling pathway can be affected in the fetal brain during critical stages of development. Abnormal PGE_2 signaling in the prenatal brain may result from changes in the maternal PGE_2 level due to deficient dietary supplementation, increased exposure to drugs, oxidative stress, infections and inflammation (Tamiji & Crawford, 2010a,b; Wong & Crawford, 2014). Maternal PGE_2 may access the developing brain through diffusion across cell membranes via its hydrophobic property or by passing across protective barriers through specific transporters summarized above. The PGE_2 pathway in the fetal brain can also be altered due to the effects of various compounds (listed below) that may be shuttled through transporters localized in the BBB and placental barrier (Table 1). Some of these transporters (including OATPs, OATs, P-gp and MRP) that normally transport endogenous compounds and nutrients have also been shown to transport exogenous drugs, toxins, estrogen-mimicking chemicals and pesticides, which could be harmful to a developing nervous system.

Environmental risk factors associated with ASDs

Exposure to various exogenous risk factors during prenatal and perinatal development can disrupt important neurodevelopmental processes, such as the patterning and growth of the brain, by altering normal gene expression and cell function (Weiss, 2000; Grandjean & Landrigan, 2006; Braw-Tal, 2010; Jurewicz *et al.*, 2013). The maternal environment can have direct consequences on the developing embryo and fetus. It is known that molecules found in the maternal system, such as lipids, can be passed into the developing embryo or fetus during pregnancy and to the growing infant through breast milk following birth (Lassek & Gaulin, 2006). Exposure to natural and manmade chemicals occurs on a daily basis through the air, soil, foods, water and consumer products. Transmission of these chemicals into the body can occur via inhalation, ingestion or contact with skin, and it has been reported that accumulations of chemicals can be found in organs (Johnson-Restrepo *et al.*, 2005) – predominately in fatty tissues (De Saeger *et al.*, 2005). A greater buildup of toxins in the mother could increase the likelihood of exposure to the developing fetus or child. Goldman &

Koduru (2000) reported that approximately 85 000 chemicals were manufactured in the USA in 2000 and, with each following year, about 2000–3000 new chemicals are reviewed by the US Environment Protection Agency (EPA). This year, approximately 2800 chemicals were used in high volumes with over £1 000 000 produced annually. They also state that nearly 80% of these chemicals lacked screening for developmental toxicity and almost half that were found in consumer products had no test data for developmental toxicity. Moreover, a study by the Environmental Working Group in the USA found that 287 of the 413 toxic substances tested were present in the umbilical cord of newborns (Houlihan *et al.*, 2005). These chemicals include heavy metals, numerous pesticides and estrogen-like endocrine-disrupting chemicals (EEDCs). One-hundred and fifty-seven of these chemicals were found to affect the brain and nervous system, and are related to developmental defects (Houlihan *et al.*, 2005). This striking information gives precedence to the investigation of potentially harmful chemicals (including air pollutants, pesticides and toxins in consumer products) that could impact the developing baby.

There is currently a lack of studies detailing the route and molecular mechanisms of how these exogenous chemicals enter into the fetus during prenatal and early development. However, the current extensive overview of the structure and development of the BBB and placental barrier reveals two potential routes: these chemicals may cross into the fetus before the formation of the protective barriers or may potentially be shuttled through the barriers by broad specificity transporters including those described above. Investigation into whether the resulting pathology in the developing brain is directly due to increased levels of these noxious compounds in the fetal brain or their metabolites is still needed. However, below, known literature on how these environmental risk factors are capable of directly affecting the PGE_2 signaling pathway during early brain development is summarized. Moreover, it is revealed how air pollutants, pesticides and toxins in consumer products may indirectly affect the PGE_2 pathway by elevating levels of inflammation, increasing levels of oxidative stress and acting as EEDCs that can affect PGE_2 signaling. Also, how these exogenous chemicals have been associated with increased risk for ASDs is discussed.

Air pollution and heavy metals

Exposure to air pollution has been shown to induce increased levels of inflammation and oxidative stress in the brains of children, adolescents and adults (Calderon-Garciduenas *et al.*, 2007, 2014; Moller *et al.*, 2014). Moreover, sustained exposure could lead to DNA damage and pathologies in the brain (Calderon-Garciduenas *et al.*, 2007, 2014; Moller *et al.*, 2014). In turn, inflammation is highly associated with increased levels of PGE_2 (Andreasson, 2010; Nakanishi & Rosenberg, 2013). PGE_2 is the most abundant prostaglandin, and can induce fever (Lawrence, 2010) and promote the production of cytokines (Legler *et al.*, 2010). Immune activation and the production of cytokines can cause disturbances in the development of neuronal pathways that have been associated with ASDs (Ashwood & Van de Water, 2004). Increased levels of oxidative stress can cause lipid peroxidation of cell membranes, including membranes of endothelial cells in the BBB, which leads to the subsequent release of second messengers like prostaglandins (de Vries *et al.*, 1996, 1997). In fact, exposure to air pollution particles and common air pollutant sulfur dioxide (SO_2) have been found to elevate PGE_2 levels in macrophages (Schneider *et al.*, 2005), lung fibroblasts (Alfaro-Moreno *et al.*, 2002) and neurons (Sang *et al.*, 2011).

Toxic air pollutants can arise from human activity, such as vehicles, factories and household cleaning solvents, and from natural activity including volcano eruptions. Toxic air pollutants are fine particles that can be found in diesel exhaust, tobacco smoke and industrial emission. They include organic compounds like styrene, and metals like mercury, lead and cadmium. Metals are of concern because they stay in the body for prolonged periods of time (Suwazono *et al.*, 2009; Wang & Du, 2013). For example, the biological half-life of cadmium in humans is between 13 and 24 years (Suwazono *et al.*, 2009; Wang & Du, 2013). They are especially dangerous to the developing brain because upon inhalation and entry into the circulation, many metals can translocate across various tissues including the BBB or can result in increased systemic levels of inflammation and oxidative stress that can also be measured in the brain (Valko *et al.*, 2005; Lopez *et al.*, 2006; Peters *et al.*, 2006; Jomova & Valko, 2011). Elevation in inflammation (Andreasson, 2010; Nakanishi & Rosenberg, 2013) and oxidative stress (de Vries *et al.*, 1996, 1997) can also lead to abnormal PGE_2 production.

A number of extensive case–control studies completed in recent years across the USA investigated the possible association of exposure to toxicants in the air and the risk of neurodevelopmental disorders such as ASDs. Each child's residential area was compared with the exposure of surrounding air pollutants, which included metals, particulates and volatile organic compounds. They report that metals (antimony, arsenic, cadmium, chromium, lead, mercury, manganese, nickel; Windham *et al.*, 2006; Roberts *et al.*, 2007, 2013; Palmer *et al.*, 2009), diesel particulates (Windham *et al.*, 2006; Roberts *et al.*, 2013; Volk *et al.*, 2014), methylene chloride (Windham *et al.*, 2006; Kalkbrenner *et al.*, 2010; Roberts *et al.*, 2013), vinyl chloride (Windham *et al.*, 2006), styrene (Kalkbrenner *et al.*, 2010) and trichloroethylene (Windham *et al.*, 2006) are associated with ASDs. Additionally, reviews from the US EPA have reported that each of these pollutants has been demonstrated to have adverse effects on the developing fetus in clinical and animal studies (EPA, 2013a). Interestingly, stronger associations were observed in boys compared with girls for most air pollutants, indicating a sex-specific interaction similar to that found in autism (Roberts *et al.*, 2013).

Porphyrin levels in the urine are often used as a biomarker for heavy metal toxicity from air pollution, including mercury and lead. Numerous independent studies have found that children with ASDs have significantly elevated levels of urinary porphyrins, which are indicative of greater symptom severity (Geier & Geier, 2006, 2007; Austin & Shandley, 2008; Geier *et al.*, 2009; Kern *et al.*, 2010, 2011; Youn *et al.*, 2010). Although measuring porphyrin levels might not be a valid diagnostic tool for ASDs on its own (Shandley *et al.*, 2014), it may help identify a subgroup of subjects with ASDs (Heyer *et al.*, 2012).

Individuals having a genetic variant in the promoter region (*rs1858830* 'C' allele) of the MET receptor tyrosine kinase gene and who are exposed to high levels of air pollutants were at a greater risk of ASDs (Volk *et al.*, 2014). A polymorphism in the delta-aminolevulinic acid dehydratase, which is associated with heavy metal toxicity and elevated levels of oxidative stress, has also been associated with autism (Rose *et al.*, 2008). This suggests that individuals with ASDs may have a decreased ability to eliminate heavy metals from the body due to a genetic etiology (Kern *et al.*, 2007). Furthermore, individuals with ASDs have impairments in detoxification and have lower levels of antioxidants, such as glutathione-s-transferase and vitamin E (Alabdali *et al.*, 2014). This may cause these individuals to be more susceptible to the accumulation of toxic metals such as mercury and lead. Altogether, many

studies report that perinatal exposure to air pollutants, in combination with genetic susceptibility, may increase risk for ASDs.

Pesticides

Pesticides are chemical agents that are distributed widely throughout our environment for two common uses: to eradicate or discourage the involvement of pests and to protect plants in agriculture. Exposure to pesticides is of great concern as they are capable of passing the placental barrier and the BBB through specific transporters, such as the OAT3 transporter described in the above sections, which normally transport PGE_2. Furthermore, many pesticides can act as EEDCs, estrogen-like compounds that can result in hormonal disturbances (Soto *et al.*, 1994; Kojima *et al.*, 2004). In rodent models, exposure to estrogen compounds have been shown to induce PGE_2 production during development causing permanent changes, such as masculinization of the brain and sexual behavior (Amateau & McCarthy, 2004). Given that pesticides are EEDCs that are capable of crossing protective barriers, it is probable that pesticides may directly or indirectly disrupt the PGE_2 lipid signaling pathway during development. Moreover, many pesticides have been found to induce oxidative stress (Abdollahi *et al.*, 2004), which can lead to abnormal increases of PGE_2 levels that may disturb sensitive periods of neurodevelopment.

The general population, including pregnant women, is exposed to these types of compounds from a wide variety of sources, including household products, food with pesticide residue or their metabolites, and air from areas where agricultural or urban spraying has occurred (Shelton *et al.*, 2012). Maternal exposure to various pesticides during pregnancy has been associated with adverse effects in cognitive development in children (Bouchard *et al.*, 2011) and increased risk of ASDs (Roberts *et al.*, 2007; Shelton *et al.*, 2012). Numerous pesticides have been shown to disrupt critical neurodevelopmental signaling pathways [such as the γ-aminobutyric acid (GABA) and acetylcholine (ACh) pathways] and important hormones, including thyroid hormones (reviewed in Shelton *et al.*, 2012). Interestingly, dysregulation of GABA, ACh and thyroid hormone signaling have been associated with ASDs (Deutsch *et al.*, 2010; Coghlan *et al.*, 2012; Khan *et al.*, 2014). Moreover, pesticides can increase levels of oxidative stress and the production of reactive oxygen species (Franco *et al.*, 2009). This leads to a decline in mitochondrial function (Cui *et al.*, 2012), which has been associated with ASDs (Rossignol & Frye, 2014). Considering that pesticides have the potential to impair neurodevelopment, the three most widely used pesticides are reviewed: organochlorine pesticides (OCPs); organophosphate pesticides (OPPs); and pyrethrins and pyrethroids (PPs).

OCPs are a group of pesticides that was used widely across the globe for agricultural purposes. Due to its low biodegradability, toxicity and incorporation into food webs, the use of these pesticides has been banned in many countries, including the USA and Canada. However, their levels remain persistent in the environment and continue to pose a risk to human health (Brun *et al.*, 2008; Crinnion, 2009). In fact, a recent study conducted in the USA found that the presence of OCPs was detected in all of the pregnant women tested (Woodruff *et al.*, 2011). In addition to their lasting presence in the environment, OCPS are able to cross the intestinal barrier, BBB and skin barrier (Escuder-Gilabert *et al.*, 2009). Examples of OCPs include dichlorodiphenyltrichloroethane, endosulfan and dicofol. Many OCPs are EEDCs, which mimic endogenous estrogen that can affect calcium signaling (Wozniak *et al.*, 2005) and PGE_2 signaling (Amateau & McCarthy, 2004). Moreover, in a large-scale case–control study on children, prenatal exposure to OCPs during the first trimester was reported to increase the risk of children developing ASDs (Roberts *et al.*, 2007). Another study identified two critical periods of vulnerability for exposure to OCPs that were associated with ASDs: from 1 month prior to conception to 5 months post-conception, and approximately 2–8 months after birth (Roberts & English, 2013).

OPPs are another group of pesticides that were originally manufactured to replace numerous banned OCPs. Examples of commonly used OPPs include chlorpyrifos, dichlorvos and malathion. OPPs act on the enzyme acetylcholinesterase and inhibit its function, causing nerve damage to unwanted pests (Costa, 2006). Unfortunately, OPPs also pose a potential risk to human health. Children whose mothers reside near application sites of OPPs during gestation were at a greater risk for ASDs (Shelton *et al.*, 2014). Furthermore, a prospective cohort study by Rauh and colleagues found that higher concentrations of chlorpyrifos in the umbilical cord plasma were associated with a greater likelihood to develop symptoms of pervasive developmental disorder by 3 years old (Rauh *et al.*, 2011). Another investigation by the same group utilized magnetic resonance imaging to show that children with increased concentrations of chlorpyrifos had structural changes in brain areas associated with attention, social cognition and receptive language processing (Rauh *et al.*, 2012). Exposure to OPPs, including those that are commonly used to deter mosquitos and fruit flies, has been shown to induce oxidative stress, mitochondrial dysfunction, and cytotoxicity to neurons and liver cells (Kaur *et al.*, 2007; Moore *et al.*, 2010). As mentioned earlier, oxidative stress and mitochondrial dysfunction has been reported in ASD cases (Rossignol & Frye, 2014). Additionally, the effects of OPPs, such as impaired cognition and altered neurochemistry, have been reported to be more severe in males than females (Levin *et al.*, 2010), comparable again to the trend found with ASDs. Similar to the findings regarding heavy metals, there have been various reports about the possibility of genetic susceptibility to OPP toxicity (reviewed in Costa, 2006). This greater susceptibility would decrease the ability to excrete OPPs and their metabolites (Costa, 2006). A study by Pasca and associates found that children with ASDs may be affected more harshly by OPPs due to relatively less active paroxonases; the enzymes responsible for metabolizing OPPs (Pasca *et al.*, 2006).

A third group of pesticides are the naturally derived pyrethrins and synthetically adapted pyrethroids. PPs have been reported by the US EPA to be found in over 3500 products in the USA (EPA, 2013b). Substantial increases in the use of PPs have been observed since 2000 when household use of OPPs had been recently banned in the USA (Williams *et al.*, 2008). Eighty-eight percent of women surveyed between 2000 and 2008 reported the use of PPs during their pregnancy, with 55% reporting high-exposure use including professional pesticide application of PPs (Williams *et al.*, 2008). Even though PPs are short-lived, their metabolites have been found in over 75% of American children and adults, and 80% in adolescence (Barr *et al.*, 2010). This suggests that utilization of PPs in daily living likely occurs in the majority of Americans. PPs and their metabolites could have toxic effects on humans as they can alter calcium signaling, induce oxidative stress and affect voltage-sensitive sodium channels (Shafer *et al.*, 2005; Soderlund, 2012). PPs have also been shown to cause neurotoxic developmental effects. For example, permethrin is a pyrethroid that is commonly found in treatment creams against lice and is also used as an agricultural pesticide. Studies show that permethrin increases oxidative stress leading to immunotoxic effects and neural apoptosis (Gabbianelli *et al.*, 2009; Shi *et al.*, 2011). Cyfluthrin is another

example of a common household pyrethroid. It was found to modulate the production and signaling of interleukin-6 and interferon-γ (Mense *et al.*, 2006), cytokines associated with ASDs (Li *et al.*, 2009). Furthermore, the authors highlighted its potential to disrupt brain development (Mense *et al.*, 2006). In addition, maternal proximity to agricultural sites (that use PPs) just prior to conception or during the third trimester was associated with an increased risk for both ASDs and developmental delay (Shelton *et al.*, 2014).

Taken together, these studies reveal that all three major groups of pesticides (OPPs, OCPs and PPs) can lead to neurodevelopmental disturbances, including increased risk for developing ASDs.

Consumer products

The daily use of consumer products potentially containing chemicals that accumulate within fatty tissues due to their lipophilic nature has become a concern for the human population. Many of these chemicals in consumer products have been shown to cross into the body and bloodstream through the skin, as well as through the protective barriers between a pregnant mother and fetus. Recent literature presented here reveals examples of chemicals that elicit physiological changes including aberrant fluctuations and dysregulation of PGE_2 signaling, hormone activity, and calcium function that may lead to developmental abnormalities. Examples of some consumer products that may contain harmful chemicals include lubricants, fire retardants, plastic containers, flooring and building materials, lotions, cosmetics, and fragrances. Persistent use of such products could potentially lead to absorption and bioaccumulation of certain compounds in the body.

Halogenated aromatic hydrocarbons (HAHs) are toxic compounds that are resistant to degradation and have been found in consumer products. Polychlorinated bisphenyls (PCBs) and polybrominated diphenyl ethers (PBDEs) are two examples of HAHs that were used in lubricants (for industrial pipelines, cables, scientific equipment, etc.) and flame retardants (compounds added to wood and manufactured materials, such as plastics and textiles), respectively (Goines & Ashwood, 2013). Despite being banned in many industrial countries after it was discovered that they can cause serious adverse health effects on both wildlife and humans, PCBs and PBDEs still remain present in human tissues and breast milk (Johnson-Restrepo *et al.*, 2005; Daniels *et al.*, 2010). Exposure to PCBs and PBDEs has been shown to increase levels of PGE_2 in uterine and placental cells leading to proinflammatory responses (Wang *et al.*, 2008; Wrobel *et al.*, 2010; Peltier *et al.*, 2012). Interestingly, the immune systems of children with ASDs react uniquely to PBDEs compared with typically developing children: peripheral blood cell samples of subjects with ASDs displayed an increased cytokine response compared with control subjects indicating an overactive immune system in ASDs (Ashwood *et al.*, 2009). This is important because the tight connection existing between the development of the immune system and CNS suggests that aberrations in immune responses may contribute to neurobehavioral disorders (Hertz-Picciotto *et al.*, 2008; Goines & Ashwood, 2013). This is in line with other studies, which have found that exposure to PCBs and PBDEs can disrupt normal neuronal development (Kimura-Kuroda *et al.*, 2007) and result in behavioral deficits observed with ASDs in the human population (Eskenazi *et al.*, 2013) and animal model (Jolous-Jamshidi *et al.*, 2010), such as social impairments. Additionally, maternal exposure to PBDEs in rats has been associated with hormonal disruptions as well as cognitive and behavioral abnormalities in the offspring (Kodavanti *et al.*, 2010). PCBs and PBDEs have also been found to cause disruptive effects on the endocrine system (Morse *et al.*, 1993; Lema *et al.*, 2008) and cause dysfunction of calcium homeostasis (Pessah *et al.*, 2010; Wayman *et al.*, 2012) – a potential marker for neurodevelopmental disorders like autism (Wayman *et al.*, 2012).

Phthalate esters, also referred to as phthalates for short, are synthetic compounds that have been used as plasticizers for a variety of consumer products, such as polyvinyl chloride (PVC) flooring material and building materials, children's toys, plastic containers, and personal care products (e.g. cosmetics, lotions and fragrances; Crinnion, 2010; Witorsch & Thomas, 2010). Phthalates found in food packaging, plastic containers, polluted soil and polluted water can contaminate our foods and beverages; this is concerning because ingesting trace amounts of phthalates may have health consequences (Schecter *et al.*, 2013; Serrano *et al.*, 2014). In fact, phthalates are widely present in foods from the USA, with high concentrations found in poultry, pork, cooking oils and cream-based dairy products (Schecter *et al.*, 2013; Serrano *et al.*, 2014). Although phthalates are short-lived chemicals that do not bio-accumulate and are rapidly excreted from the body (Heudorf *et al.*, 2007), they still present a potential risk to human health because they are EEDCs. As EEDCs, they mimic endogenous estrogen by activating estrogen receptors and by acting as an antagonist to androgen receptors (Takeuchi *et al.*, 2005; Sharpe, 2008). Moreover, exposure to phthalates has been shown to disrupt the levels of prostaglandins, including PGE_2, in uterine and amniotic cells (Pavan *et al.*, 2001; Wang *et al.*, 2010). It has been found through retrospective case and clinical studies that phthalate exposure is linked to behavioral abnormalities and developmental disorders, including attention-deficit hyperactivity disorder (ADHD) and ASDs (Larsson *et al.*, 2009; Engel *et al.*, 2010; Miodovnik *et al.*, 2011; Testa *et al.*, 2012). A study conducted in Sweden investigating potential harmful indoor environmental factors found that if PVC flooring was present in the parents' or children's room, which is a source of airborne phthalates, the child was at an increased risk of developing ASDs compared with wood flooring (Larsson *et al.*, 2009). Prenatal exposure to phthalates during the third trimester of pregnancy (determined by urine samples) has been associated with adverse effects on childhood behavior and executive functioning, with behavioral outcomes commonly found in children with ADHD (Engel *et al.*, 2010). Because phthalates are expelled quickly from the body, detection of phthalates in the urine indicates that daily phthalate exposure is likely occurring. Another study also measuring the urine samples of pregnant women in their third trimester found that phthalate exposure was associated with deficits in social behavior, communication, social awareness and social cognition (Miodovnik *et al.*, 2011). In a study examining the phthalate levels in children, a significant increase in the urinary concentrations of phthalate metabolites was detected in children with ASDs compared with control children (Testa *et al.*, 2012). Strikingly, the authors of this study were able to identify subjects with ASDs with 91.1% specificity through the measurement of phthalate metabolite, 5-oxo-MEHP. In summary, these studies provide evidence that prenatal and postnatal exposure to phthalates has been associated with behavioral differences and developmental disorders like ASDs.

Bisphenol A (BPA) has been used to make epoxy resins and polycarbonate plastics, both of which are used in many household products, including reusable plastic food containers, the internal lining of tin cans, food-packaging materials and cash register receipts (vom Saal & Hughes, 2005; Biedermann *et al.*, 2010). BPA can enter the body through the skin, eating or drinking contaminated sources, hand-to-mouth contact, and manufacturer workplace expo-

sure (Biedermann *et al.*, 2010; CDC, 2013). Leaching of BPA molecules from consumer product sources has been shown to be increased when washing polycarbonate plastics and heating BPA-containing containers to sterilize foods (Howdeshell *et al.*, 2003; Kang *et al.*, 2003). Furthermore, it has been shown that BPA can leach from landfills into surrounding ecosystems, affecting drinking and bathing water (Coors *et al.*, 2003). In a national health and nutrition examination study conducted by the Centre for Disease Control and Prevention in the USA in 2003–2004, nearly all individuals tested had BPA in the urine, suggesting widespread BPA exposure (CDC, 2013). Similarly, a study conducted by Statistics Canada in 2009–2011 found that BPA was detected in the urine of 95% of Canadians between the ages of 3 and 79 years, with the highest levels of BPA measured in children between the ages of 3 and 5, and 6 and 11 years (Statistics-Canada, 2013). Because BPA has been found to be rapidly metabolized (Volkel *et al.*, 2002), this suggests that human exposure occurs in a continuous manner most likely from multiple sources. BPA has been found in various human body fluids, such as fetal serum and full-term amniotic fluid (Ikezuki *et al.*, 2002), indicating that BPA has the ability to pass through the placenta that acts as a maternal–fetal protective barrier.

Exposure to BPA has been shown to alter the human uterine microenvironment by disrupting PGE_2 production in the endometrium and corpus luteum, which could disturb embryonic and fetal development (Romani *et al.*, 2013; Mannelli *et al.*, 2014). BPA is also known as a common EEDC (vom Saal & Hughes, 2005) that can exert its toxic effects at low human-relevant doses (Welshons *et al.*, 2003). Studies completed on mouse and rat models found that prenatal and perinatal exposure to BPA can affect the offspring by upregulating the immune response (Yoshino *et al.*, 2004), altering social behaviors and expression of estrogen receptors (Wolstenholme *et al.*, 2012), increasing hyperactive behavior (Ishido *et al.*, 2004), impairing neural pathways involving fear and learning (Negishi *et al.*, 2004), decreasing levels of Shh, a crucial developmental signaling molecule, and affecting dopaminergic neuron development (Miyagawa *et al.*, 2007), and changing levels of DNA methyltransferases in the cortex, suggesting the possibility of epigenetic and transgenerational effects (Kundakovic *et al.*, 2013). A clinical prospective study found that gestational BPA exposure was associated with deficits in behavioral and emotional regulation in children at 3 years old (Braun *et al.*, 2011). Postnatal exposure to BPA in animal model studies revealed that exposure led to elevated levels of reactive oxygen species and lipid peroxidation, and decreased levels of antioxidant enzymes (Chitra *et al.*, 2003), higher estrogen receptor levels in the brain (Aloisi *et al.*, 2001), and increased calcium signaling in hippocampal neurons (Tanabe *et al.*, 2006). To summarize, prenatal and postnatal BPA exposure was found to be toxic by altering gene expression, disrupting immunological and neural pathways, and altering behaviors later in life.

Cosmetics are another group of consumer products that possess chemicals that may be harmful to human health. For example, cosmetic eyelash growth products often include ingredients bimatoprost or dechloro ethylcloprostenolamide, which are prostaglandin analogs that can activate prostaglandin receptors (Alm *et al.*, 2008; Choy & Lin, 2008; Toris *et al.*, 2008), and thus are capable of disrupting normal prostaglandin signaling. Furthermore, siloxanes and parabens are chemicals that are often found in cosmetics that have been contested as substances that put human health at risk. Siloxanes (cyclic and linear) are used in cosmetics as spreading agents (Nair & Cosmetic Ingredients Review Expert, 2003). They are of concern because they can accumulate in fatty issues, and are EEDCs that are able to elicit estrogenic activity (Luu & Hutter, 2001; McKim *et al.*, 2001; He *et al.*, 2003) and indirectly disrupt PGE_2 levels (Amateau & McCarthy, 2004). Additionally, they may cause adverse effects on the nervous system by disrupting normal dopamine neurotransmission (Alexeeff, 2007). Parabens are largely used as antimicrobial

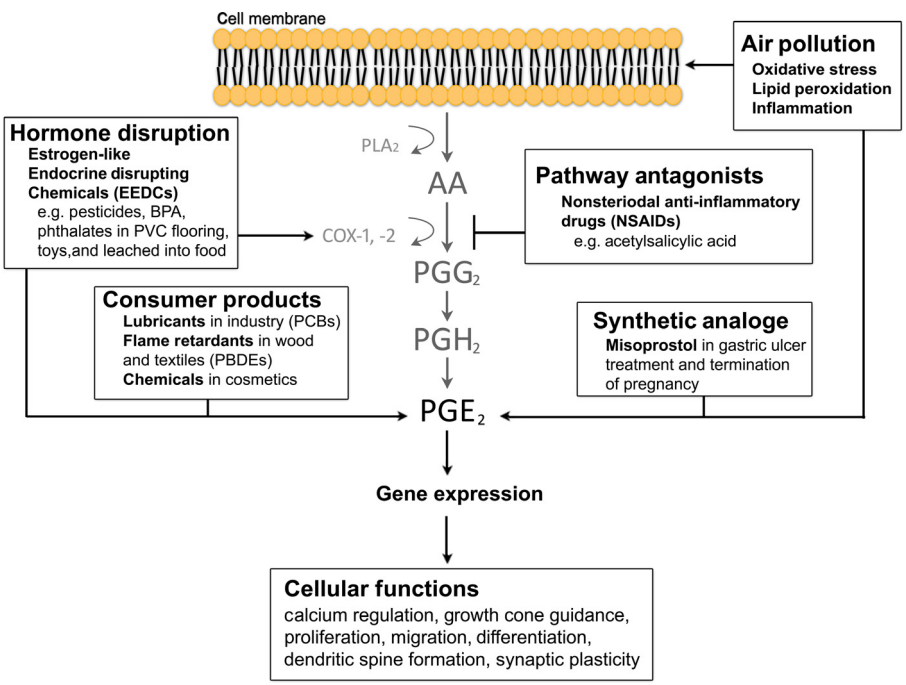

FIG. 4. Environmental factors, such as exposure to chemicals in drugs, air pollution, pesticides and consumer products, can disrupt normal lipid signaling pathways, such as the PGE_2 pathway. They can act as analogs, antagonists and EEDCs that interfere with PGE_2 signaling and result in altered gene expression, thereby influencing the function and development of brain cells.

preservatives in products such as cosmetics and pharmaceuticals, and on foods (Crinnion, 2010), and can also increase estrogenic activity (Darbre & Harvey, 2008). As mentioned earlier, elevated estrogenic activity can disturb regular PGE_2 signaling during development. Taken altogether, a variety of chemicals that can be found in the environment and in consumer products are capable of bio-accumulating in human tissue and are capable of altering the signaling of important developmental pathways, such as the lipid mediator PGE_2 signaling pathway (Fig. 4). In addition to the chemicals mentioned above, Health Canada has published a science-based document, an 'Ingredient Hotlist' containing a list of prohibited and restricted substances for use in cosmetics due to their hazardous properties (Canada, 2014). Given that these chemicals are considered dangerous to the health of an adult, they could produce profound disturbances on the developing brain, which starts prenatally and continues into adolescence.

Conclusions

In closing, lipids and lipid signaling pathways, such as PGE_2, are crucial in the development of the brain. Protective barriers, such as the BBB and the placental barrier, develop from early pregnancy on and have transporters embedded in them to allow healthy development of the fetus by shuttling nutrients between the mother and fetus, and into the CNS of the fetus. However, these transporters have also been found to transport exogenous chemicals that disturb PGE_2 signaling. The studies summarized in this review provide evidence that exposure to particular chemicals in the environment, air, food and consumer products is potentially harmful, as exposure can affect key developing pathways, including the PGE_2 pathway. These studies also reveal that prenatal exposure to air pollution, heavy metals, pesticides and toxic substances in consumer products may trigger atypical brain development and lead to neural pathologies such as ASDs. This indicates that these chemicals can cross the protective barriers between the mother and the fetus during the critical period when toxicants become capable of eliciting disruptive neurodevelopmental effects in the brain. This collection of work justifies the need to further investigate the long-term effects of common chemicals and products. Although general risk information of chemicals is available through the Integrated Risk Information System (EPA, 2015), specific chemical concentration ranges that pose a risk to health during prenatal development and during chronic exposure in humans remains to be established. Moreover, the accumulative effects of exposure to numerous chemicals are not known. Until the risks of these toxins are fully understood, it is crucial to be an educated consumer and to limit exposure to these environmental risk factors especially during prenatal and perinatal development when the brain is most vulnerable.

Abbreviations

ABC, ATP-binding cassette; ACh, acetylcholine; ADHD, attention-deficit hyperactivity disorder; ASD, autism spectrum disorder; ATP, adenosine triphosphate; BBB, blood–brain barrier; BPA, bisphenol A; COX, cyclooxygenase; E, embryonic day; EEDC, estrogen-like endocrine-disrupting chemical; EPA, Environmental Protection Agency; GABA, γ-aminobutyric acid; HAH, halogenated aromatic hydrocarbon; MRP, multidrug resistance-associated protein; MT, monozygotic twin; NSAID, non-steroidal anti-inflammatory drug; OAT, organic anion transporter; OATP, organic anion transporting polypeptide; OCP, organochlorine pesticide; OPP, organophosphate pesticide; P, postnatal day; PBDE, polybrominated diphenyl ether; PCB, polychlorinated bisphenyl; PGE_2, prostaglandin E2; P-gp, P-glycoprotein; PGT, prostaglandin-transporter; PP, pyrethrin and pyrethroid; PVC, polyvinyl chloride; Shh, sonic hedgehog; SLC, solute-linked carrier; TJ, tight junction.

References

Abbott, N.J. (2002) Astrocyte-endothelial interactions and blood-brain barrier permeability. *J. Anat.*, **200**, 629–638.

Abbott, N.J., Patabendige, A.A., Dolman, D.E., Yusof, S.R. & Begley, D.J. (2010) Structure and function of the blood-brain barrier. *Neurobiol. Dis.*, **37**, 13–25.

Abbott, N.J., Ronnback, L. & Hansson, E. (2006) Astrocyte-endothelial interactions at the blood-brain barrier. *Nat. Rev. Neurosci.*, **7**, 41–53.

Abdollahi, M., Ranjbar, A., Shadnia, S., Nikfar, S. & Rezaie, A. (2004) Pesticides and oxidative stress: a review. *Med. Sci. Monitor*, **10**, RA141–147.

Adibhatla, R.M. & Hatcher, J.F. (2008) Altered lipid metabolism in brain injury and disorders. *Sub-Cellular Biochem.*, **49**, 241–268.

Alabdali, A., Al-Ayadhi, L. & El-Ansary, A. (2014) A key role for an impaired detoxification mechanism in the etiology and severity of autism spectrum disorders. *Behav. Brain Funct.*, **10**, 14.

Alebouyeh, M., Takeda, M., Onozato, M.L., Tojo, A., Noshiro, R., Hasannejad, H., Inatomi, J., Narikawa, S., Huang, X.L., Khamdang, S., Anzai, N. & Endou, H. (2003) Expression of human organic anion transporters in the choroid plexus and their interactions with neurotransmitter metabolites. *J. Pharmacol. Sci.*, **93**, 430–436.

Aleksunes, L.M., Cui, Y. & Klaassen, C.D. (2008) Prominent expression of xenobiotic efflux transporters in mouse extraembryonic fetal membranes compared with placenta. *Drug Metab. Dispos.*, **36**, 1960–1970.

Alexeeff, G. (2007) OEHHA Toxicity Data Review: Decamethylcyclopentasiloxane (D5). [Internet] Available from: http://www.arb.ca.gov/toxics/dryclean/oehhad5review.pdf.

Alfaro-Moreno, E., Martinez, L., Garcia-Cuellar, C., Bonner, J.C., Murray, J.C., Rosas, I., Rosales, S.P. & Osornio-Vargas, A.R. (2002) Biologic effects induced in vitro by PM10 from three different zones of Mexico City. *Environ. Health Persp.*, **110**, 715–720.

Alm, A., Grierson, I. & Shields, M.B. (2008) Side effects associated with prostaglandin analog therapy. *Surv. Ophthalmol.*, **53**(Suppl 1), S93–105.

Aloisi, A.M., Della Seta, D., Ceccarelli, I. & Farabollini, F. (2001) Bisphenol-A differently affects estrogen receptors-alpha in estrous-cycling and lactating female rats. *Neurosci. Lett.*, **310**, 49–52.

Alvarez, J.I., Dodelet-Devillers, A., Kebir, H., Ifergan, I., Fabre, P.J., Terouz, S., Sabbagh, M., Wosik, K., Bourbonniere, L., Bernard, M., van Horssen, J., de Vries, H.E., Charron, F. & Prat, A. (2011) The Hedgehog pathway promotes blood-brain barrier integrity and CNS immune quiescence. *Science*, **334**, 1727–1731.

Amateau, S.K. & McCarthy, M.M. (2002) A novel mechanism of dendritic spine plasticity involving estradiol induction of prostaglandin-E2. *J. Neurosci.*, **22**, 8586–8596.

Amateau, S.K. & McCarthy, M.M. (2004) Induction of PGE2 by estradiol mediates developmental masculinization of sex behavior. *Nat. Neurosci.*, **7**, 643–650.

Andersen, S.L. (2003) Trajectories of brain development: point of vulnerability or window of opportunity? *Neurosci. Biobehav. R.*, **27**, 3–18.

Andreasson, K. (2010) Emerging roles of PGE2 receptors in models of neurological disease. *Prostag. Oth. Lipid M.*, **91**, 104–112.

Anstrom, J.A., Thore, C.R., Moody, D.M. & Brown, W.R. (2007) Immunolocalization of tight junction proteins in blood vessels in human germinal matrix and cortex. *Histochem. Cell Biol.*, **127**, 205–213.

Armulik, A., Genove, G. & Betsholtz, C. (2011) Pericytes: developmental, physiological, and pathological perspectives, problems, and promises. *Dev. Cell*, **21**, 193–215.

Armulik, A., Genove, G., Mae, M., Nisancioglu, M.H., Wallgard, E., Niaudet, C., He, L., Norlin, J., Lindblom, P., Strittmatter, K., Johansson, B.R. & Betsholtz, C. (2010) Pericytes regulate the blood-brain barrier. *Nature*, **468**, 557–561.

Ashwood, P., Schauer, J., Pessah, I.N. & Van de Water, J. (2009) Preliminary evidence of the in vitro effects of BDE-47 on innate immune responses in children with autism spectrum disorders. *J. Neuroimmunol.*, **208**, 130–135.

Ashwood, P. & Van de Water, J. (2004) A review of autism and the immune response. *Clin. Dev. Immunol.*, **11**, 165–174.

Austin, D.W. & Shandley, K. (2008) An investigation of porphyrinuria in Australian children with autism. *J. Tox. Env. Health A*, **71**, 1349–1351.

Aye, I.L. & Keelan, J.A. (2013) Placental ABC transporters, cellular toxicity and stress in pregnancy. *Chem. Biol. Interact.*, **203**, 456–466.

Bahn, A., Ljubojevic, M., Lorenz, H., Schultz, C., Ghebremedhin, E., Ugele, B., Sabolic, I., Burckhardt, G. & Hagos, Y. (2005) Murine renal organic anion transporters mOAT1 and mOAT3 facilitate the transport of neuroactive tryptophan metabolites. *Am. J. Physiol. Cell Physiol.*, **289**, C1075–1084.

Ballabh, P., Braun, A. & Nedergaard, M. (2004) The blood-brain barrier: an overview: structure, regulation, and clinical implications. *Neurobiol. Dis.*, **16**, 1–13.

Banerjee, S. & Bhat, M.A. (2007) Neuron-glial interactions in blood-brain barrier formation. *Annu. Rev. Neurosci.*, **30**, 235–258.

Banerjee, S., Riordan, M. & Bhat, M.A. (2014) Genetic aspects of autism spectrum disorders: insights from animal models. *Front. Cell. Neurosci.*, **8**, 58.

Bar, T. & Wolff, J.R. (1972) The formation of capillary basement membranes during internal vascularization of the rat's cerebral cortex. *Z Zellforsch Mik. Ana.*, **133**, 231–248.

Barr, D.B., Olsson, A.O., Wong, L.Y., Udunka, S., Baker, S.E., Whitehead, R.D., Magsumbol, M.S., Williams, B.L. & Needham, L.L. (2010) Urinary concentrations of metabolites of pyrethroid insecticides in the general U.S. population: National Health and Nutrition Examination Survey 1999-2002. *Environ. Health Persp.*, **118**, 742–748.

Bauer, H.C., Bauer, H., Lametschwandtner, A., Amberger, A., Ruiz, P. & Steiner, M. (1993) Neovascularization and the appearance of morphological characteristics of the blood-brain barrier in the embryonic mouse central nervous system. *Brain Res. Dev. Brain Res.*, **75**, 269–278.

Behravan, J. & Piquette-Miller, M. (2007) Drug transport across the placenta, role of the ABC drug efflux transporters. *Expert Opin. Drug Met*, **3**, 819–830.

Belmonte, M.K. & Carper, R.A. (2006) Monozygotic twins with Asperger syndrome: differences in behaviour reflect variations in brain structure and function. *Brain Cogn.*, **61**, 110–121.

Berezowski, V., Landry, C., Dehouck, M.P., Cecchelli, R. & Fenart, L. (2004) Contribution of glial cells and pericytes to the mRNA profiles of P-glycoprotein and multidrug resistance-associated proteins in an in vitro model of the blood-brain barrier. *Brain Res.*, **1018**, 1–9.

Bhattacharjee, J., Ietta, F., Romagnoli, R., Bechi, N., Caniggia, I. & Paulesu, L. (2012) ABC transporters in human placenta and their role in maternal-fetal cholesterol transfer: ABCA1 candidate target. In Zheng, J. (Ed.), *Recent Advances in Research on the Human Placenta*. InTech, pp. 335–354. [Internet] Available: http://www.intechopen.com/books/recent-advances-in-research-on-the-human-placenta/abc-transporters-in-human-placenta-and-their-role-in-maternal-fetal-cholesterol-transfer-abca1-candi.

Bhogal, R., Wong, C., Li, H. & Crawford, D. (2013) Effects of prostaglandin-E2 on expression of wnt-target genes during critical period of mouse brain development. Program No. 244.19/T15. 2013 Neuroscience Meeting Planner. Society for Neuroscience, New Orleans, LA. [Internet] Available from: http://www.sfn.org/~/media/SfN/Documents/Annual%20Meeting/FinalProgram/NS2013/FullAbstractPDFs_2013/AbstractPDFs_Poster_-Sun_PM.ashx.

Biedermann, S., Tschudin, P. & Grob, K. (2010) Transfer of bisphenol A from thermal printer paper to the skin. *Anal. Bioanal. Chem.*, **398**, 571–576.

Bloxam, D.L., Bax, C.M. & Bax, B.E. (1997) Culture of syncytiotrophoblast for the study of human placental transfer. Part I: isolation and purification of cytotrophoblast. *Placenta*, **18**, 93–98.

Blumberg, SJ, Bramlett, MD & Kogan, E.A. (2013) Changes in prevalence of parent-reported autism spectrum disorder in school-aged U.S. children: 2007-2012. *Natl. Health Stat. Rep.*, **65**, 1–11.

Bohm, H.V., Stewart, M.G. & Healy, A.M. (2013) On the Autistic Spectrum Disorder concordance rates of twins and non-twin siblings. *Med. Hypotheses*, **81**, 789–791.

Bouchard, M.F., Chevrier, J., Harley, K.G., Kogut, K., Vedar, M., Calderon, N., Trujillo, C., Johnson, C., Bradman, A., Barr, D.B. & Eskenazi, B. (2011) Prenatal exposure to organophosphate pesticides and IQ in 7-year-old children. *Environ. Health Persp.*, **119**, 1189–1195.

Braun, J.M., Kalkbrenner, A.E., Calafat, A.M., Yolton, K., Ye, X., Dietrich, K.N. & Lanphear, B.P. (2011) Impact of early-life bisphenol A exposure on behavior and executive function in children. *Pediatrics*, **128**, 873–882.

Braw-Tal, R. (2010) Endocrine disruptors and timing of human exposure. *Pediatr. Endocrinol. Rev.*, **8**, 41–46.

Brett, K.E., Ferraro, Z.M., Yockell-Lelievre, J., Gruslin, A. & Adamo, K.B. (2014) Maternal-fetal nutrient transport in pregnancy pathologies: the role of the placenta. *Int. J. Mol. Sci.*, **15**, 16153–16185.

Briz, O., Serrano, M.A., MacIas, R.I., Gonzalez-Gallego, J. & Marin, J.J. (2003) Role of organic anion-transporting polypeptides, OATP-A, OATP-C and OATP-8, in the human placenta-maternal liver tandem excretory pathway for foetal bilirubin. *Biochem. J.*, **371**, 897–905.

Bronger, H., Konig, J., Kopplow, K., Steiner, H.H., Ahmadi, R., Herold-Mende, C., Keppler, D. & Nies, A.T. (2005) ABCC drug efflux pumps and organic anion uptake transporters in human gliomas and the blood-tumor barrier. *Cancer Res.*, **65**, 11419–11428.

Brun, G.L., MacDonald, R.M., Verge, J. & Aube, J. (2008) Long-term atmospheric deposition of current-use and banned pesticides in Atlantic Canada; 1980-2000. *Chemosphere*, **71**, 314–327.

Buchanan, F.G. & DuBois, R.N. (2006) Connecting COX-2 and Wnt in cancer. *Cancer Cell*, **9**, 6–8.

Burton, G.J., Jauniaux, E. & Watson, A.L. (1999) Maternal arterial connections to the placental intervillous space during the first trimester of human pregnancy: the Boyd collection revisited. *Am. J. Obstet. Gynecol.*, **181**, 718–724.

Calderon-Garciduenas, L., Franco-Lira, M., Torres-Jardon, R., Henriquez-Roldan, C., Barragan-Mejia, G., Valencia-Salazar, G., Gonzalez-Maciel, A., Reynoso-Robles, R., Villarreal-Calderon, R. & Reed, W. (2007) Pediatric respiratory and systemic effects of chronic air pollution exposure: nose, lung, heart, and brain pathology. *Toxicol. Pathol.*, **35**, 154–162.

Calderon-Garciduenas, L., Kulesza, R.J., Doty, R.L., D'Angiulli, A. & Torres-Jardon, R. (2014) Megacities air pollution problems: Mexico City Metropolitan Area critical issues on the central nervous system pediatric impact. *Environ. Res.*, **137C**, 157–169.

Calderon, F. & Kim, H.Y. (2004) Docosahexaenoic acid promotes neurite growth in hippocampal neurons. *J. Neurochem.*, **90**, 979–988.

Carlson, S.E. (2009) Early determinants of development: a lipid perspective. *Am. J. Clin. Nutr.*, **89**, 1523S–1529S.

Centers for Disease Control and Prevention (CDC) (2012) Prevalence of autism spectrum disorders–Autism and Developmental Disabilities Monitoring Network, 14 sites, United States, 2008. *MMWR Surveill. Summ.*, **61**, 1–19.

Centers for Disease Control and Prevention (CDC) (2013) National Biomonitoring Program: BPA Factsheet. [Internet] Available from: http://www.cdc.gov/biomonitoring/BisphenolA_FactSheet.html.

Centers for Disease Control and Prevention (CDC) (2014) Prevalence of autism spectrum disorder among children aged 8 years - autism and developmental disabilities monitoring network, 11 sites, United States, 2010. *MMWR Surveill. Summ.*, **63**, 1–21.

Cervos-Navarro, J., Kannuki, S. & Nakagawa, Y. (1988) Blood-brain barrier (BBB). Review from morphological aspect. *Histol. Histopathol.*, **3**, 203–213.

Chan, S.Y., Martin-Santos, A., Loubiere, L.S., Gonzalez, A.M., Stieger, B., Logan, A., McCabe, C.J., Franklyn, J.A. & Kilby, M.D. (2011) The expression of thyroid hormone transporters in the human fetal cerebral cortex during early development and in N-Tera-2 neurodifferentiation. *J. Physiol.*, **589**, 2827–2845.

Charron, F. & Tessier-Lavigne, M. (2005) Novel brain wiring functions for classical morphogens: a role as graded positional cues in axon guidance. *Development*, **132**, 2251–2262.

Chitra, K.C., Latchoumycandane, C. & Mathur, P.P. (2003) Induction of oxidative stress by bisphenol A in the epididymal sperm of rats. *Toxicology*, **185**, 119–127.

Choi, K., Zhuang, H., Crain, B. & Dore, S. (2008) Expression and localization of prostaglandin transporter in Alzheimer disease brains and age-matched controls. *J. Neuroimmunol.*, **195**, 81–87.

Choy, I. & Lin, S. (2008) Eyelash enhancement properties of topical dechloro ethylcloprostenolamide. *J. Cosmet. Laser Ther.*, **10**, 110–113.

Coghlan, S., Horder, J., Inkster, B., Mendez, M.A., Murphy, D.G. & Nutt, D.J. (2012) GABA system dysfunction in autism and related disorders: from synapse to symptoms. *Neurosci. Biobehav. Rev.*, **36**, 2044–2055.

Coors, A., Jones, P.D., Giesy, J.P. & Ratte, H.T. (2003) Removal of estrogenic activity from municipal waste landfill leachate assessed with a bioassay based on reporter gene expression. *Environ. Sci. Technol.*, **37**, 3430–3434.

Costa, L.G. (2006) Current issues in organophosphate toxicology. *Clin. Chim. Acta*, **366**, 1–13.

Crinnion, W.J. (2009) Chlorinated pesticides: threats to health and importance of detection. *Altern. Med. Rev.*, **14**, 347–359.

Crinnion, W.J. (2010) Toxic effects of the easily avoidable phthalates and parabens. *Altern. Med. Rev.*, **15**, 190–196.

Cui, H., Kong, Y. & Zhang, H. (2012) Oxidative stress, mitochondrial dysfunction, and aging. *J. Signal Transd.*, **2012**, 646354.

Dallas, S., Miller, D.S. & Bendayan, R. (2006) Multidrug resistance-associated proteins: expression and function in the central nervous system. *Pharmacol. Rev.*, **58**, 140–161.

Daneman, R., Agalliu, D., Zhou, L., Kuhnert, F., Kuo, C.J. & Barres, B.A. (2009) Wnt/beta-catenin signaling is required for CNS, but not non-CNS, angiogenesis. *Proc. Natl. Acad. Sci. USA*, **106**, 641–646.

Daneman, R., Zhou, L., Agalliu, D., Cahoy, J.D., Kaushal, A. & Barres, B.A. (2010a) The mouse blood-brain barrier transcriptome: a new resource

for understanding the development and function of brain endothelial cells. *PLoS ONE*, **5**, e13741.
Daneman, R., Zhou, L., Kebede, A.A. & Barres, B.A. (2010b) Pericytes are required for blood-brain barrier integrity during embryogenesis. *Nature*, **468**, 562–566.
Daniels, J.L., Pan, I.J., Jones, R., Anderson, S., Patterson, D.G. Jr., Needham, L.L. & Sjodin, A. (2010) Individual characteristics associated with PBDE levels in U.S. human milk samples. *Environ. Health Persp.*, **118**, 155–160.
Darbre, P.D. & Harvey, P.W. (2008) Paraben esters: review of recent studies of endocrine toxicity, absorption, esterase and human exposure, and discussion of potential human health risks. *J. Appl. Toxicol.*, **28**, 561–578.
De Saeger, S., Sergeant, H., Piette, M., Bruneel, N., Van de Voorder, W. & Van Peteghem, C. (2005) Monitoring of polychlorinated biphenyls in Belgian human adipose tissue samples. *Chemosphere*, **58**, 953–960.
Decleves, X., Regina, A., Laplanche, J.L., Roux, F., Boval, B., Launay, J.M. & Scherrmann, J.M. (2000) Functional expression of P-glycoprotein and multidrug resistance-associated protein (Mrp1) in primary cultures of rat astrocytes. *J. Neurosci. Res.*, **60**, 594–601.
Deutsch, S.I., Urbano, M.R., Neumann, S.A., Burket, J.A. & Katz, E. (2010) Cholinergic abnormalities in autism: is there a rationale for selective nicotinic agonist interventions? *Clin. Neuropharmacol.*, **33**, 114–120.
Dombrowski, S.M., Desai, S.Y., Marroni, M., Cucullo, L., Goodrich, K., Bingaman, W., Mayberg, M.R., Bengez, L. & Janigro, D. (2001) Overexpression of multiple drug resistance genes in endothelial cells from patients with refractory epilepsy. *Epilepsia*, **42**, 1501–1506.
Ek, C.J., Dziegielewska, K.M., Habgood, M.D. & Saunders, N.R. (2012) Barriers in the developing brain and Neurotoxicology. *Neurotoxicology*, **33**, 586–604.
Ek, C.J., Wong, A., Liddelow, S.A., Johansson, P.A., Dziegielewska, K.M. & Saunders, N.R. (2010) Efflux mechanisms at the developing brain barriers: ABC-transporters in the fetal and postnatal rat. *Toxicol. Lett.*, **197**, 51–59.
Engel, S.M., Miodovnik, A., Canfield, R.L., Zhu, C., Silva, M.J., Calafat, A.M. & Wolff, M.S. (2010) Prenatal phthalate exposure is associated with childhood behavior and executive functioning. *Environ. Health Persp.*, **118**, 565–571.
Escuder-Gilabert, L., Villanueva-Camanas, R.M., Sagrado, S. & Medina-Hernandez, M.J. (2009) Permeability and toxicological profile estimation of organochlorine compounds by biopartitioning micellar chromatography. *Biomed. Chromatogr.*, **23**, 382–389.
Eskenazi, B., Chevrier, J., Rauch, S.A., Kogut, K., Harley, K.G., Johnson, C., Trujillo, C., Sjodin, A. & Bradman, A. (2013) In utero and childhood polybrominated diphenyl ether (PBDE) exposures and neurodevelopment in the CHAMACOS study. *Environ. Health Persp.*, **121**, 257–262.
Evans, T. (2009) Fishing for a WNT-PGE2 link: beta-catenin is caught in the stem cell net-work. *Cell Stem Cell*, **4**, 280–282.
Evseenko, D., Paxton, J.W. & Keelan, J.A. (2006) Active transport across the human placenta: impact on drug efficacy and toxicity. *Expert Opin. Drug Metab. Toxicol.*, **2**, 51–69.
Fisher, M. (2009) Pericyte signaling in the neurovascular unit. *Stroke*, **40**, S13–15.
da Fonseca, A.C., Matias, D., Garcia, C., Amaral, R., Geraldo, L.H., Freitas, C. & Lima, F.R. (2014) The impact of microglial activation on blood-brain barrier in brain diseases. *Front. Cell. Neurosci.*, **8**, 362.
Franco, R., Sanchez-Olea, R., Reyes-Reyes, E.M. & Panayiotidis, M.I. (2009) Environmental toxicity, oxidative stress and apoptosis: menage a trois. *Mutat. Res.*, **674**, 3–22.
Frazier, T.W., Thompson, L., Youngstrom, E.A., Law, P., Hardan, A.Y., Eng, C. & Morris, N. (2014) A twin study of heritable and shared environmental contributions to autism. *J. Autism Dev. Disord.*, **44**, 2013–2025.
Fujiyoshi, M., Ohtsuki, S., Hori, S., Tachikawa, M. & Terasaki, T. (2007) 24S-hydroxycholesterol induces cholesterol release from choroid plexus epithelial cells in an apical- and apoE isoform-dependent manner concomitantly with the induction of ABCA1 and ABCG1 expression. *J. Neurochem.*, **100**, 968–978.
Gabbianelli, R., Falcioni, M.L., Nasuti, C., Cantalamessa, F., Imada, I. & Inoue, M. (2009) Effect of permethrin insecticide on rat polymorphonuclear neutrophils. *Chem. Biol. Interact.*, **182**, 245–252.
Garbett, K., Ebert, P.J., Mitchell, A., Lintas, C., Manzi, B., Mirnics, K. & Persico, A.M. (2008) Immune transcriptome alterations in the temporal cortex of subjects with autism. *Neurobiol. Dis.*, **30**, 303–311.
Geier, D.A. & Geier, M.R. (2006) A prospective assessment of porphyrins in autistic disorders: a potential marker for heavy metal exposure. *Neurotox. Res.*, **10**, 57–64.
Geier, D.A. & Geier, M.R. (2007) A prospective study of mercury toxicity biomarkers in autistic spectrum disorders. *J. Tox. Env. Health A*, **70**, 1723–1730.
Geier, D.A., Kern, J.K. & Geier, M.R. (2009) A prospective blinded evaluation of urinary porphyrins verses the clinical severity of autism spectrum disorders. *J. Tox. Env. Health A*, **72**, 1585–1591.
Girardin, F. (2006) Membrane transporter proteins: a challenge for CNS drug development. *Dialog. Clin. Neurosci.*, **8**, 311–321.
Goessling, W., North, T.E., Loewer, S., Lord, A.M., Lee, S., Stoick-Cooper, C.L., Weidinger, G., Puder, M., Daley, G.Q., Moon, R.T. & Zon, L.I. (2009) Genetic interaction of PGE2 and Wnt signaling regulates developmental specification of stem cells and regeneration. *Cell*, **136**, 1136–1147.
Goines, P.E. & Ashwood, P. (2013) Cytokine dysregulation in autism spectrum disorders (ASD): possible role of the environment. *Neurotoxicol. Teratol.*, **36**, 67–81.
Goldman, L.R. & Koduru, S. (2000) Chemicals in the environment and developmental toxicity to children: a public health and policy perspective. *Environ. Health Persp.*, **108**(Suppl 3), 443–448.
Grandjean, P. & Landrigan, P.J. (2006) Developmental neurotoxicity of industrial chemicals. *Lancet*, **368**, 2167–2178.
Grube, M., Kock, K., Karner, S., Reuther, S., Ritter, C.A., Jedlitschky, G. & Kroemer, H.K. (2006) Modification of OATP2B1-mediated transport by steroid hormones. *Mol. Pharmacol.*, **70**, 1735–1741.
Guo, H., Hu, Z., Zhao, J. & Xia, K. (2011) Genetics of autism spectrum disorders. *Zhong Nan Da Xue Xue Bao*, **36**, 703–711.
Gupta, S., Ellis, S.E., Ashar, F.N., Moes, A., Bader, J.S., Zhan, J., West, A.B. & Arking, D.E. (2014) Transcriptome analysis reveals dysregulation of innate immune response genes and neuronal activity-dependent genes in autism. *Nat. Commun.*, **5**, 5748.
Hagenbuch, B. & Meier, P.J. (2004) Organic anion transporting polypeptides of the OATP/ SLC21 family: phylogenetic classification as OATP/ SLCO superfamily, new nomenclature and molecular/functional properties. *Pflug. Arch.*, **447**, 653–665.
Hagenbuch, B. & Stieger, B. (2013) The SLCO (former SLC21) superfamily of transporters. *Mol. Aspects Med.*, **34**, 396–412.
Hall, L. & Kelley, E. (2014) The contribution of epigenetics to understanding genetic factors in autism. *Autism*, **18**, 872–881.
Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe, T., Miller, J., Fedele, A., Collins, J., Smith, K., Lotspeich, L., Croen, L.A., Ozonoff, S., Lajonchere, C., Grether, J.K. & Risch, N. (2011) Genetic heritability and shared environmental factors among twin pairs with autism. *Arch. Gen. Psychiat.*, **68**, 1095–1102.
Hamilton, J.A., Johnson, R.A., Corkey, B. & Kamp, F. (2001) Fatty acid transport: the diffusion mechanism in model and biological membranes. *J. Mol. Neurosci.*, **16**, 99–108.
Hartz, A.M. & Bauer, B. (2011) ABC transporters in the CNS - an inventory. *Curr. Pharm. Biotechnol.*, **12**, 656–673.
Hashimoto, T., Tayama, M., Murakawa, K., Yoshimoto, T., Miyazaki, M., Harada, M. & Kuroda, Y. (1995) Development of the brainstem and cerebellum in autistic patients. *J. Autism Dev. Disord.*, **25**, 1–18.
Hawkins, R.A., O'Kane, R.L., Simpson, I.A. & Vina, J.R. (2006) Structure of the blood-brain barrier and its role in the transport of amino acids. *J. Nutr.*, **136**, 218S–226S.
He, B., Rhodes-Brower, S., Miller, M.R., Munson, A.E., Germolec, D.R., Walker, V.R., Korach, K.S. & Meade, B.J. (2003) Octamethylcyclotetrasiloxane exhibits estrogenic activity in mice via ERalpha. *Toxicol. Appl. Pharmacol.*, **192**, 254–261.
Health Canada - Government of Canada (2014) Cosmetic Ingredient Hotlist: Prohibited and Restricted Ingredients - Consumer Product Safety. [Internet] Available from: http://www.hc-sc.gc.ca/cps-spc/cosmet-person/hot-list-critique/index-eng.php.
Herbert, M.R. (2010) Contributions of the environment and environmentally vulnerable physiology to autism spectrum disorders. *Curr. Opin. Neurol.*, **23**, 103–110.
Hertz-Picciotto, I. & Delwiche, L. (2009) The rise in autism and the role of age at diagnosis. *Epidemiology*, **20**, 84–90.
Hertz-Picciotto, I., Park, H.Y., Dostal, M., Kocan, A., Trnovec, T. & Sram, R. (2008) Prenatal exposures to persistent and non-persistent organic compounds and effects on immune system development. *Basic Clin. Pharmacol.*, **102**, 146–154.
Heudorf, U., Mersch-Sundermann, V. & Angerer, J. (2007) Phthalates: toxicology and exposure. *Int. J. Hyg. Envir. Heal.*, **210**, 623–634.
Heyer, N.J., Echeverria, D. & Woods, J.S. (2012) Disordered porphyrin metabolism: a potential biological marker for autism risk assessment. *Autism Res.*, **5**, 84–92.

Holden, K.R. (2008) Malnutrition and brain development: a review. In Engel, J.J. (Ed.), *Neurologic Consequences of Malnutrition*. Demos, New York, pp. 19–35.

Houlihan, J., Kropp, T., Wiles, R., Gray, S., Campbell, C. & Greene, A. (2005) Body burden: the pollution in newborns. *Environ. Work. Group*. [Internet] Available: http://www.ewg.org/research/body-burden-pollution-newborns.

Howdeshell, K.L., Peterman, P.H., Judy, B.M., Taylor, J.A., Orazio, C.E., Ruhlen, R.L., Vom Saal, F.S. & Welshons, W.V. (2003) Bisphenol A is released from used polycarbonate animal cages into water at room temperature. *Environ. Health Persp.*, **111**, 1180–1187.

Huber, R.D., Gao, B., Sidler Pfandler, M.A., Zhang-Fu, W., Leuthold, S., Hagenbuch, B., Folkers, G., Meier, P.J. & Stieger, B. (2007) Characterization of two splice variants of human organic anion transporting polypeptide 3A1 isolated from human brain. *Am. J. Physiol. Cell Physiol.*, **292**, C795–806.

Ikezuki, Y., Tsutsumi, O., Takai, Y., Kamei, Y. & Taketani, Y. (2002) Determination of bisphenol A concentrations in human biological fluids reveals significant early prenatal exposure. *Hum. Reprod.*, **17**, 2839–2841.

Innis, S.M. (2007) Dietary (n-3) fatty acids and brain development. *J. Nutr.*, **137**, 855–859.

Ishido, M., Masuo, Y., Kunimoto, M., Oka, S. & Morita, M. (2004) Bisphenol A causes hyperactivity in the rat concomitantly with impairment of tyrosine hydroxylase immunoreactivity. *J. Neurosci. Res.*, **76**, 423–433.

Jacobson, M. (1991) *Developmental Neurobiology*. Plenum, New York.

Jiang, J., Ganesh, T., Du, Y., Thepchatri, P., Rojas, A., Lewis, I., Kurtkaya, S., Li, L., Qui, M., Serrano, G., Shaw, R., Sun, A. & Dingledine, R. (2010) Neuroprotection by selective allosteric potentiators of the EP2 prostaglandin receptor. *Proc. Natl. Acad. Sci. USA*, **107**, 2307–2312.

Johnson-Restrepo, B., Kannan, K., Rapaport, D.P. & Rodan, B.D. (2005) Polybrominated diphenyl ethers and polychlorinated biphenyls in human adipose tissue from New York. *Environ. Sci. Technol.*, **39**, 5177–5182.

Jolous-Jamshidi, B., Cromwell, H.C., McFarland, A.M. & Meserve, L.A. (2010) Perinatal exposure to polychlorinated biphenyls alters social behaviors in rats. *Toxicol. Lett.*, **199**, 136–143.

Jomova, K. & Valko, M. (2011) Advances in metal-induced oxidative stress and human disease. *Toxicology*, **283**, 65–87.

Jurewicz, J., Polanska, K. & Hanke, W. (2013) Chemical exposure early in life and the neurodevelopment of children–an overview of current epidemiological evidence. *Ann. Agr. Env. Med.*, **20**, 465–486.

Kalkbrenner, A.E., Daniels, J.L., Chen, J.C., Poole, C., Emch, M. & Morrissey, J. (2010) Perinatal exposure to hazardous air pollutants and autism spectrum disorders at age 8. *Epidemiology*, **21**, 631–641.

Kang, J.H., Kito, K. & Kondo, F. (2003) Factors influencing the migration of bisphenol A from cans. *J. Food Prot.*, **66**, 1444–1447.

Kanherkar, R.R., Bhatia-Dey, N. & Csoka, A.B. (2014) Epigenetics across the human lifespan. *Front. Cell Dev. Biol.*, **2**, 49.

Kates, W.R., Burnette, C.P., Eliez, S., Strunge, L.A., Kaplan, D., Landa, R., Reiss, A.L. & Pearlson, G.D. (2004) Neuroanatomic variation in monozygotic twin pairs discordant for the narrow phenotype for autism. *Am. J. Psychiat.*, **161**, 539–546.

Kates, W.R., Mostofsky, S.H., Zimmerman, A.W., Mazzocco, M.M., Landa, R., Warsofsky, I.S., Kaufmann, W.E. & Reiss, A.L. (1998) Neuroanatomical and neurocognitive differences in a pair of monozygous twins discordant for strictly defined autism. *Ann. Neurol.*, **43**, 782–791.

Kaur, P., Radotra, B., Minz, R.W. & Gill, K.D. (2007) Impaired mitochondrial energy metabolism and neuronal apoptotic cell death after chronic dichlorvos (OP) exposure in rat brain. *Neurotoxicology*, **28**, 1208–1219.

Kern, J.K., Geier, D.A., Adams, J.B. & Geier, M.R. (2010) A biomarker of mercury body-burden correlated with diagnostic domain specific clinical symptoms of autism spectrum disorder. *Biometals*, **23**, 1043–1051.

Kern, J.K., Geier, D.A., Adams, J.B., Mehta, J.A., Grannemann, B.D. & Geier, M.R. (2011) Toxicity biomarkers in autism spectrum disorder: a blinded study of urinary porphyrins. *Pediatr. Int.*, **53**, 147–153.

Kern, J.K., Grannemann, B.D., Trivedi, M.H. & Adams, J.B. (2007) Sulfhydryl-reactive metals in autism. *J. Tox. Env. Health A*, **70**, 715–721.

Khan, A., Harney, J.W., Zavacki, A.M. & Sajdel-Sulkowska, E.M. (2014) Disrupted brain thyroid hormone homeostasis and altered thyroid hormone-dependent brain gene expression in autism spectrum disorders. *J. Physiol. Pharmacol.*, **65**, 257–272.

Kim, W.S., Guillemin, G.J., Glaros, E.N., Lim, C.K. & Garner, B. (2006) Quantitation of ATP-binding cassette subfamily-A transporter gene expression in primary human brain cells. *NeuroReport*, **17**, 891–896.

Kim, Y.S. & Leventhal, B.L. (2015) Genetic epidemiology and insights into interactive genetic and environmental effects in autism spectrum disorders. *Biol. Psychiat.*, **77**, 66–74.

Kimura-Kuroda, J., Nagata, I. & Kuroda, Y. (2007) Disrupting effects of hydroxy-polychlorinated biphenyl (PCB) congeners on neuronal development of cerebellar Purkinje cells: a possible causal factor for developmental brain disorders? *Chemosphere*, **67**, S412–420.

Klaassen, C.D. & Aleksunes, L.M. (2010) Xenobiotic, bile acid, and cholesterol transporters: function and regulation. *Pharmacol. Rev.*, **62**, 1–96.

Kniesel, U., Risau, W. & Wolburg, H. (1996) Development of blood-brain barrier tight junctions in the rat cortex. *Brain Res. Dev. Brain Res.*, **96**, 229–240.

Koch, H., Huh, S.E., Elsen, F.P., Carroll, M.S., Hodge, R.D., Bedogni, F., Turner, M.S., Hevner, R.F. & Ramirez, J.M. (2010) Prostaglandin E2-induced synaptic plasticity in neocortical networks of organotypic slice cultures. *J. Neurosci.*, **30**, 11678–11687.

Kodavanti, P.R., Coburn, C.G., Moser, V.C., MacPhail, R.C., Fenton, S.E., Stoker, T.E., Rayner, J.L., Kannan, K. & Birnbaum, L.S. (2010) Developmental exposure to a commercial PBDE mixture, DE-71: neurobehavioral, hormonal, and reproductive effects. *Toxicol. Sci.*, **116**, 297–312.

Koepsell, H. (2013) The SLC22 family with transporters of organic cations, anions and zwitterions. *Mol. Aspects Med.*, **34**, 413–435.

Kojima, H., Katsura, E., Takeuchi, S., Niiyama, K. & Kobayashi, K. (2004) Screening for estrogen and androgen receptor activities in 200 pesticides by in vitro reporter gene assays using Chinese hamster ovary cells. *Environ. Health Persp.*, **112**, 524–531.

Koldamova, R.P., Lefterov, I.M., Ikonomovic, M.D., Skoko, J., Lefterov, P.I., Isanski, B.A., DeKosky, S.T. & Lazo, J.S. (2003) 22R-hydroxycholesterol and 9-cis-retinoic acid induce ATP-binding cassette transporter A1 expression and cholesterol efflux in brain cells and decrease amyloid beta secretion. *J. Biol. Chem.*, **278**, 13244–13256.

Kratzer, I., Liddelow, S.A., Saunders, N.R., Dziegielewska, K.M., Strazielle, N. & Ghersi-Egea, J.F. (2013) Developmental changes in the transcriptome of the rat choroid plexus in relation to neuroprotection. *Fluids Barriers CNS*, **10**, 25.

Kundakovic, M., Gudsnuk, K., Franks, B., Madrid, J., Miller, R.L., Perera, F.P. & Champagne, F.A. (2013) Sex-specific epigenetic disruption and behavioral changes following low-dose in utero bisphenol A exposure. *Proc. Natl. Acad. Sci. USA*, **110**, 9956–9961.

Kusuhara, H. & Sugiyama, Y. (2005) Active efflux across the blood-brain barrier: role of the solute carrier family. *NeuroRx*, **2**, 73–85.

Larsson, M., Weiss, B., Janson, S., Sundell, J. & Bornehag, C.G. (2009) Associations between indoor environmental factors and parental-reported autistic spectrum disorders in children 6-8 years of age. *Neurotoxicology*, **30**, 822–831.

Lassek, W.D. & Gaulin, S.J. (2006) Changes in body fat distribution in relation to parity in American women: a covert form of maternal depletion. *Am. J. Phys. Anthropol.*, **131**, 295–302.

Lawrence, G.D. (2010) *The Fats of Life: Essential Fatty Acids in Health and Disease*. Rutgers University Press, New Brunswick.

Lee, G., Dallas, S., Hong, M. & Bendayan, R. (2001) Drug transporters in the central nervous system: brain barriers and brain parenchyma considerations. *Pharmacol. Rev.*, **53**, 569–596.

Leggas, M., Adachi, M., Scheffer, G.L., Sun, D., Wielinga, P., Du, G., Mercer, K.E., Zhuang, Y., Panetta, J.C., Johnston, B., Scheper, R.J., Stewart, C.F. & Schuetz, J.D. (2004) Mrp4 confers resistance to topotecan and protects the brain from chemotherapy. *Mol. Cell. Biol.*, **24**, 7612–7621.

Legler, D.F., Bruckner, M., Uetz-von Allmen, E. & Krause, P. (2010) Prostaglandin E2 at new glance: novel insights in functional diversity offer therapeutic chances. *Int. J. Biochem. Cell B.*, **42**, 198–201.

Lema, S.C., Dickey, J.T., Schultz, I.R. & Swanson, P. (2008) Dietary exposure to 2,2',4,4'-tetrabromodiphenyl ether (PBDE-47) alters thyroid status and thyroid hormone-regulated gene transcription in the pituitary and brain. *Environ. Health Persp.*, **116**, 1694–1699.

Lenz, K.M., Nugent, B.M., Haliyur, R. & McCarthy, M.M. (2013) Microglia are essential to masculinization of brain and behavior. *J. Neurosci.*, **33**, 2761–2772.

Levin, E.D., Timofeeva, O.A., Yang, L., Petro, A., Ryde, I.T., Wrench, N., Seidler, F.J. & Slotkin, T.A. (2010) Early postnatal parathion exposure in rats causes sex-selective cognitive impairment and neurotransmitter defects which emerge in aging. *Behav. Brain Res.*, **208**, 319–327.

Li, X., Chauhan, A., Sheikh, A.M., Patil, S., Chauhan, V., Li, X.M., Ji, L., Brown, T. & Malik, M. (2009) Elevated immune response in the brain of autistic patients. *J. Neuroimmunol.*, **207**, 111–116.

Lichtenstein, P., Carlstrom, E., Rastam, M., Gillberg, C. & Anckarsater, H. (2010) The genetics of autism spectrum disorders and related neuropsychiatric disorders in childhood. *Am. J. Psychiat.*, **167**, 1357–1363.

Lopez, E., Arce, C., Oset-Gasque, M.J., Canadas, S. & Gonzalez, M.P. (2006) Cadmium induces reactive oxygen species generation and lipid peroxidation in cortical neurons in culture. *Free Radic. Biol. Med.*, **40**, 940–951.

Loscher, W. & Potschka, H. (2005) Role of drug efflux transporters in the brain for drug disposition and treatment of brain diseases. *Prog. Neurobiol.*, **76**, 22–76.

Loubiere, L.S., Vasilopoulou, E., Bulmer, J.N., Taylor, P.M., Stieger, B., Verrey, F., McCabe, C.J., Franklyn, J.A., Kilby, M.D. & Chan, S.Y. (2010) Expression of thyroid hormone transporters in the human placenta and changes associated with intrauterine growth restriction. *Placenta*, **31**, 295–304.

Luu, H.M. & Hutter, J.C. (2001) Bioavailability of octamethylcyclotetrasiloxane (D(4)) after exposure to silicones by inhalation and implantation. *Environ. Health Persp.*, **109**, 1095–1101.

Mannelli, C., Szòstek, A., Carotenuto, C., Ietta, F., Romagnoli, R., Piotrowska-Tomala, K., Paulesu, L. & Skarzynski, D. (2014) Environmental chemicals and reproduction: how Bisphenol A triggers a pro-inflammatory response in endometrial stromal cells. *Soc. Reprod. Fertility*, Edinburgh. [Internet] Available: http://www.srf-reproduction.org/Portals/0/Conferences/Abstracts/SRF_2014/SRF_2014O001.pdf.

McKim, J.M. Jr., Wilga, P.C., Breslin, W.J., Plotzke, K.P., Gallavan, R.H. & Meeks, R.G. (2001) Potential estrogenic and antiestrogenic activity of the cyclic siloxane octamethylcyclotetrasiloxane (D4) and the linear siloxane hexamethyldisiloxane (HMDS) in immature rats using the uterotrophic assay. *Toxicol. Sci.*, **63**, 37–46.

Meek, S.E., Lemery-Chalfant, K., Jahromi, L.B. & Valiente, C. (2013) A review of gene-environment correlations and their implications for autism: a conceptual model. *Psychol. Rev.*, **120**, 497–521.

Meier-Abt, F., Mokrab, Y. & Mizuguchi, K. (2005) Organic anion transporting polypeptides of the OATP/SLCO superfamily: identification of new members in nonmammalian species, comparative modeling and a potential transport mode. *J. Membrane Biol.*, **208**, 213–227.

Mense, S.M., Sengupta, A., Lan, C., Zhou, M., Bentsman, G., Volsky, D.J., Whyatt, R.M., Perera, F.P. & Zhang, L. (2006) The common insecticides cyfluthrin and chlorpyrifos alter the expression of a subset of genes with diverse functions in primary human astrocytes. *Toxicol. Sci.*, **93**, 125–135.

Miller, D.S., Nobmann, S.N., Gutmann, H., Toeroek, M., Drewe, J. & Fricker, G. (2000) Xenobiotic transport across isolated brain microvessels studied by confocal microscopy. *Mol. Pharmacol.*, **58**, 1357–1367.

Miodovnik, A., Engel, S.M., Zhu, C., Ye, X., Soorya, L.V., Silva, M.J., Calafat, A.M. & Wolff, M.S. (2011) Endocrine disruptors and childhood social impairment. *Neurotoxicology*, **32**, 261–267.

Mitchell, S.R., Reiss, A.L., Tatusko, D.H., Ikuta, I., Kazmerski, D.B., Botti, J.A., Burnette, C.P. & Kates, W.R. (2009) Neuroanatomic alterations and social and communication deficits in monozygotic twins discordant for autism disorder. *Am. J. Psychiat.*, **166**, 917–925.

Miyagawa, K., Narita, M., Narita, M., Niikura, K., Akama, H., Tsurukawa, Y. & Suzuki, T. (2007) Changes in central dopaminergic systems with the expression of Shh or GDNF in mice perinatally exposed to bisphenol-A. *Nihon Shinkei Seishin Yakurigaku Zasshi*, **27**, 69–75.

Mizee, M.R., Wooldrik, D., Lakeman, K.A., van het Hof, B., Drexhage, J.A., Geerts, D., Bugiani, M., Aronica, E., Mebius, R.E., Prat, A., de Vries, H.E. & Reijerkerk, A. (2013) Retinoic acid induces blood-brain barrier development. *J. Neurosci.*, **33**, 1660–1671.

Moller, P., Danielsen, P.H., Karottki, D.G., Jantzen, K., Roursgaard, M., Klingberg, H., Jensen, D.M., Christophersen, D.V., Hemmingsen, J.G., Cao, Y. & Loft, S. (2014) Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles. *Mutat. Res. Rev.* , **762C**, 133–166.

Mollgard, K. & Saunders, N.R. (1975) Complex tight junctions of epithelial and of endothelial cells in early foetal brain. *J. Neurocytol.*, **4**, 453–468.

Moore, K.L. & Persaud, T.V.N. (1998) *Before We Are Born: Essentials of Embryology and Birth Defects*. Saunders, Philadelphia.

Moore, P.D., Yedjou, C.G. & Tchounwou, P.B. (2010) Malathion-induced oxidative stress, cytotoxicity, and genotoxicity in human liver carcinoma (HepG2) cells. *Environ. Toxicol.*, **25**, 221–226.

Morse, D.C., Groen, D., Veerman, M., van Amerongen, C.J., Koeter, H.B., Smits van Prooije, A.E., Visser, T.J., Koeman, J.H. & Brouwer, A. (1993) Interference of polychlorinated biphenyls in hepatic and brain thyroid hormone metabolism in fetal and neonatal rats. *Toxicol. Appl. Pharmacol.*, **122**, 27–33.

Muhle, R., Trentacoste, S.V. & Rapin, I. (2004) The genetics of autism. *Pediatrics*, **113**, e472–486.

Nair, B. & Cosmetic Ingredients Review Expert, P. (2003) Final report on the safety assessment of stearoxy dimethicone, dimethicone, methicone, amino bispropyl dimethicone, aminopropyl dimethicone, amodimethicone, amodimethicone hydroxystearate, behenoxy dimethicone, C24-28 alkyl methicone, C30-45 alkyl methicone, C30-45 alkyl dimethicone, cetearyl methicone, cetyl dimethicone, dimethoxysilyl ethylenediaminopropyl dimethicone, hexyl methicone, hydroxypropyldimethicone, stearamidopropyl dimethicone, stearyl dimethicone, stearyl methicone, and vinyldimethicone. *Int. J. Toxicol.*, **22**(Suppl 2), 11–35.

Nakanishi, M. & Rosenberg, D.W. (2013) Multifaceted roles of PGE2 in inflammation and cancer. *Semin. Immunopathol.*, **35**, 123–137.

Nayak, D., Roth, T.L. & McGavern, D.B. (2014) Microglia development and function. *Annu. Rev. Immunol.*, **32**, 367–402.

Negishi, T., Kawasaki, K., Suzaki, S., Maeda, H., Ishii, Y., Kyuwa, S., Kuroda, Y. & Yoshikawa, Y. (2004) Behavioral alterations in response to fear-provoking stimuli and tranylcypromine induced by perinatal exposure to bisphenol A and nonylphenol in male rats. *Environ. Health Persp.*, **112**, 1159–1164.

Nies, A.T., Jedlitschky, G., Konig, J., Herold-Mende, C., Steiner, H.H., Schmitt, H.P. & Keppler, D. (2004) Expression and immunolocalization of the multidrug resistance proteins, MRP1-MRP6 (ABCC1-ABCC6), in human brain. *Neuroscience*, **129**, 349–360.

Obermeier, B., Daneman, R. & Ransohoff, R.M. (2013) Development, maintenance and disruption of the blood-brain barrier. *Nat. Med.*, **19**, 1584–1596.

Palmer, R.F., Blanchard, S. & Wood, R. (2009) Proximity to point sources of environmental mercury release as a predictor of autism prevalence. *Health Place*, **15**, 18–24.

Pasca, S.P., Nemes, B., Vlase, L., Gagyi, C.E., Dronca, E., Miu, A.C. & Dronca, M. (2006) High levels of homocysteine and low serum paraoxonase 1 arylesterase activity in children with autism. *Life Sci.*, **78**, 2244–2248.

Pavan, B., Biondi, C., Ferretti, M.E., Lunghi, L. & Paganetto, G. (2001) Phthalic acid mimics 17beta-estradiol actions in WISH cells. *Toxicol. Lett.*, **118**, 157–164.

Pavlova, A., Sakurai, H., Leclercq, B., Beier, D.R., Yu, A.S. & Nigam, S.K. (2000) Developmentally regulated expression of organic ion transporters NKT (OAT1), OCT1, NLT (OAT2), and Roct. *Am. J. Physiol. Renal. Physiol.*, **278**, F635–643.

Pelphrey, K.A., Yang, D.Y. & McPartland, J.C. (2014) Building a social neuroscience of autism spectrum disorder. *Curr. Top. Behav. Neurosci.*, **16**, 215–233.

Peltier, M.R., Klimova, N.G., Arita, Y., Gurzenda, E.M., Murthy, A., Chawala, K., Lerner, V., Richardson, J. & Hanna, N. (2012) Polybrominated diphenyl ethers enhance the production of proinflammatory cytokines by the placenta. *Placenta*, **33**, 745–749.

Perry, V.H., Nicoll, J.A. & Holmes, C. (2010) Microglia in neurodegenerative disease. *Nat. Rev. Neurol.*, **6**, 193–201.

Pessah, I.N., Cherednichenko, G. & Lein, P.J. (2010) Minding the calcium store: ryanodine receptor activation as a convergent mechanism of PCB toxicity. *Pharmacol. Ther.*, **125**, 260–285.

Peters, A., Veronesi, B., Calderon-Garciduenas, L., Gehr, P., Chen, L.C., Geiser, M., Reed, W., Rothen-Rutishauser, B., Schurch, S. & Schulz, H. (2006) Translocation and potential neurological effects of fine and ultrafine particles a critical update. *Part Fibre Toxicol.*, **3**, 13.

Qin, Y. & Sato, T.N. (1995) Mouse multidrug resistance 1a/3 gene is the earliest known endothelial cell differentiation marker during blood-brain barrier development. *Dev. Dyn.*, **202**, 172–180.

Rauh, V., Arunajadai, S., Horton, M., Perera, F., Hoepner, L., Barr, D.B. & Whyatt, R. (2011) Seven-year neurodevelopmental scores and prenatal exposure to chlorpyrifos, a common agricultural pesticide. *Environ. Health Persp.*, **119**, 1196–1201.

Rauh, V.A., Perera, F.P., Horton, M.K., Whyatt, R.M., Bansal, R., Hao, X., Liu, J., Barr, D.B., Slotkin, T.A. & Peterson, B.S. (2012) Brain anomalies in children exposed prenatally to a common organophosphate pesticide. *Proc. Natl. Acad. Sci. USA*, **109**, 7871–7876.

Reichel, C., Gao, B., Van Montfoort, J., Cattori, V., Rahner, C., Hagenbuch, B., Stieger, B., Kamisako, T. & Meier, P.J. (1999) Localization and function of the organic anion-transporting polypeptide Oatp2 in rat liver. *Gastroenterology*, **117**, 688–695.

Rizwan, A.N. & Burckhardt, G. (2007) Organic anion transporters of the SLC22 family: biopharmaceutical, physiological, and pathological roles. *Pharm. Res.*, **24**, 450–470.

Roberts, A.L., Lyall, K., Hart, J.E., Laden, F., Just, A.C., Bobb, J.F., Koenen, K.C., Ascherio, A. & Weisskopf, M.G. (2013) Perinatal air pollutant exposures and autism spectrum disorder in the children of Nurses' Health Study II participants. *Environ. Health Persp.*, **121**, 978–984.

Roberts, E.M. & English, P.B. (2013) Bayesian modeling of time-dependent vulnerability to environmental hazards: an example using autism and pesticide data. *Stat. Med.*, **32**, 2308–2319.

Roberts, E.M., English, P.B., Grether, J.K., Windham, G.C., Somberg, L. & Wolff, C. (2007) Maternal residence near agricultural pesticide applications and autism spectrum disorders among children in the California Central Valley. *Environ. Health Persp.*, **115**, 1482–1489.

Roberts, L.M., Black, D.S., Raman, C., Woodford, K., Zhou, M., Haggerty, J.E., Yan, A.T., Cwirla, S.E. & Grindstaff, K.K. (2008) Subcellular localization of transporters along the rat blood-brain barrier and blood-cerebral-spinal fluid barrier by in vivo biotinylation. *Neuroscience*, **155**, 423–438.

Roediger, M., Miosge, N. & Gersdorff, N. (2010) Tissue distribution of the laminin beta1 and beta2 chain during embryonic and fetal human development. *J. Mol. Histol.*, **41**, 177–184.

Romani, F., Tropea, A., Scarinci, E., Dello Russo, C., Lisi, L., Catino, S., Lanzone, A. & Apa, R. (2013) Endocrine disruptors and human corpus luteum: in vitro effects of phenols on luteal cells function. *J. Environ. Sci. Heal C*, **31**, 170–180.

Ronald, A. & Hoekstra, R. (2014) Progress in understanding the causes of autism spectrum disorders and autistic traits: twin studies from 1977 to the present day. In Rhee, S.H. & Ronald, A. (Eds), *Behavior Genetics of Psychopathology*. Springer, New York, pp. 33–65.

Rose, S., Melnyk, S., Savenka, A., Hubanks, A., Cleves, S.J.M. & James, S.J. (2008) The frequency of polymorphisms affecting lead and mercury toxicity among children with Autism. *Am. J. Biochem. Biotechnol.*, **4**, 85–94.

Rosenberg, R.E., Law, J.K., Yenokyan, G., McGready, J., Kaufmann, W.E. & Law, P.A. (2009) Characteristics and concordance of autism spectrum disorders among 277 twin pairs. *Arch. Pediatr. Adolesc. Med.*, **163**, 907–914.

Rossignol, D.A. & Frye, R.E. (2014) Evidence linking oxidative stress, mitochondrial dysfunction, and inflammation in the brain of individuals with autism. *Front. Physiol.*, **5**, 150.

Rossignol, D.A., Genuis, S.J. & Frye, R.E. (2014) Environmental toxicants and autism spectrum disorders: a systematic review. *Transl. Psychiat.*, **4**, e360.

Roth, M., Obaidat, A. & Hagenbuch, B. (2012) OATPs, OATs and OCTs: the organic anion and cation transporters of the SLCO and SLC22A gene superfamilies. *Br. J. Pharmacol.*, **165**, 1260–1287.

Sang, N., Yun, Y., Yao, G.Y., Li, H.Y., Guo, L. & Li, G.K. (2011) SO(2)-induced neurotoxicity is mediated by cyclooxygenases-2-derived prostaglandin E(2) and its downstream signaling pathway in rat hippocampal neurons. *Toxicol. Sci.*, **124**, 400–413.

Saunders, N.R., Knott, G.W. & Dziegielewska, K.M. (2000) Barriers in the immature brain. *Cell. Mol. Neurobiol.*, **20**, 29–40.

Saunders, N.R., Liddelow, S.A. & Dziegielewska, K.M. (2012) Barrier mechanisms in the developing brain. *Front. Pharmacol.*, **3**, 46.

Sauvageot, C.M. & Stiles, C.D. (2002) Molecular mechanisms controlling cortical gliogenesis. *Curr. Opin. Neurobiol.*, **12**, 244–249.

Scafidi, S., Douglas, R.M., Farahani, R., Banasiak, K.J. & Haddad, G.G. (2007) Prostaglandin transporter expression in mouse brain during development and in response to hypoxia. *Neuroscience*, **146**, 1150–1157.

Schecter, A., Lorber, M., Guo, Y., Wu, Q., Yun, S.H., Kannan, K., Hommel, M., Imran, N., Hynan, L.S., Cheng, D., Colacino, J.A. & Birnbaum, L.S. (2013) Phthalate concentrations and dietary exposure from food purchased in New York State. *Environ. Health Persp.*, **121**, 473–494.

Schneider, J.C., Card, G.L., Pfau, J.C. & Holian, A. (2005) Air pollution particulate SRM 1648 causes oxidative stress in RAW 264.7 macrophages leading to production of prostaglandin E2, a potential Th2 mediator. *Inhalation Toxicol.*, **17**, 871–877.

Schulze, C. & Firth, J.A. (1992) Interendothelial junctions during blood-brain barrier development in the rat: morphological changes at the level of individual tight junctional contacts. *Brain Res. Dev. Brain Res.*, **69**, 85–95.

Schumacher, U. & Mollgard, K. (1997) The multidrug-resistance P-glycoprotein (Pgp, MDR1) is an early marker of blood-brain barrier development in the microvessels of the developing human brain. *Histochem. Cell Biol.*, **108**, 179–182.

Schwenk, R.W., Holloway, G.P., Luiken, J.J., Bonen, A. & Glatz, J.F. (2010) Fatty acid transport across the cell membrane: regulation by fatty acid transporters. *Prostag. Leukot. Ess.*, **82**, 149–154.

Serrano, S.E., Braun, J., Trasande, L., Dills, R. & Sathyanarayana, S. (2014) Phthalates and diet: a review of the food monitoring and epidemiology data. *Environ. Health*, **13**, 43.

Shafer, T.J., Meyer, D.A. & Crofton, K.M. (2005) Developmental neurotoxicity of pyrethroid insecticides: critical review and future research needs. *Environ. Health Persp.*, **113**, 123–136.

Shandley, K., Austin, D.W. & Bhowmik, J.L. (2014) Are urinary porphyrins a valid diagnostic biomarker of autism spectrum disorder? *Autism Res.*, **7**, 535–542.

Sharpe, R.M. (2008) "Additional" effects of phthalate mixtures on fetal testosterone production. *Toxicol. Sci.*, **105**, 1–4.

Shelton, J.F., Geraghty, E.M., Tancredi, D.J., Delwiche, L.D., Schmidt, R.J., Ritz, B., Hansen, R.L. & Hertz-Picciotto, I. (2014) Neurodevelopmental disorders and prenatal residential proximity to agricultural pesticides: the CHARGE study. *Environ. Health Persp.*, **122**, 1103–1109.

Shelton, J.F., Hertz-Picciotto, I. & Pessah, I.N. (2012) Tipping the balance of autism risk: potential mechanisms linking pesticides and autism. *Environ. Health Persp.*, **120**, 944–951.

Shi, X., Gu, A., Ji, G., Li, Y., Di, J., Jin, J., Hu, F., Long, Y., Xia, Y., Lu, C., Song, L., Wang, S. & Wang, X. (2011) Developmental toxicity of cypermethrin in embryo-larval stages of zebrafish. *Chemosphere*, **85**, 1010–1016.

Soderlund, D.M. (2012) Molecular mechanisms of pyrethroid insecticide neurotoxicity: recent advances. *Arch. Toxicol.*, **86**, 165–181.

Soto, A.M., Chung, K.L. & Sonnenschein, C. (1994) The pesticides endosulfan, toxaphene, and dieldrin have estrogenic effects on human estrogen-sensitive cells. *Environ. Health Persp.*, **102**, 380–383.

St-Pierre, M.V., Hagenbuch, B., Ugele, B., Meier, P.J. & Stallmach, T. (2002) Characterization of an organic anion-transporting polypeptide (OATP-B) in human placenta. *J. Clin. Endocrinol. Metab.*, **87**, 1856–1863.

St-Pierre, M.V., Serrano, M.A., Macias, R.I., Dubs, U., Hoechli, M., Lauper, U., Meier, P.J. & Marin, J.J. (2000) Expression of members of the multidrug resistance protein family in human term placenta. *Am. J. Physiol. Regul. Integr. Comp. Physiol.*, **279**, R1495–1503.

Statistics Canada - Government of Canada (2013) Bisphenol A concentrations in Canadians, 2009 to 2011. [Internet] Available from: http://www.statcan.gc.ca/pub/82-625-x/2013001/article/11778-eng.htm.

Stewart, P.A. & Hayakawa, E.M. (1987) Interendothelial junctional changes underlie the developmental 'tightening' of the blood-brain barrier. *Brain Res.*, **429**, 271–281.

Stiles, J. & Jernigan, T.L. (2010) The basics of brain development. *Neuropsychol. Rev.*, **20**, 327–348.

Stilp, R.L., Gernsbacher, M.A., Schweigert, E.K., Arneson, C.L. & Goldsmith, H.H. (2010) Genetic variance for autism screening items in an unselected sample of toddler-age twins. *J. Am. Acad. Child Psy.*, **49**, 267–276.

Suwazono, Y., Kido, T., Nakagawa, H., Nishijo, M., Honda, R., Kobayashi, E., Dochi, M. & Nogawa, K. (2009) Biological half-life of cadmium in the urine of inhabitants after cessation of cadmium exposure. *Biomarkers*, **14**, 77–81.

Syme, M.R., Paxton, J.W. & Keelan, J.A. (2004) Drug transfer and metabolism by the human placenta. *Clin. Pharmacokinet.*, **43**, 487–514.

Tachikawa, M., Ozeki, G., Higuchi, T., Akanuma, S., Tsuji, K. & Hosoya, K. (2012) Role of the blood-cerebrospinal fluid barrier transporter as a cerebral clearance system for prostaglandin E(2) produced in the brain. *J. Neurochem.*, **123**, 750–760.

Tachikawa, M., Watanabe, M., Hori, S., Fukaya, M., Ohtsuki, S., Asashima, T. & Terasaki, T. (2005) Distinct spatio-temporal expression of ABCA and ABCG transporters in the developing and adult mouse brain. *J. Neurochem.*, **95**, 294–304.

Takeuchi, S., Iida, M., Kobayashi, S., Jin, K., Matsuda, T. & Kojima, H. (2005) Differential effects of phthalate esters on transcriptional activities via human estrogen receptors alpha and beta, and androgen receptor. *Toxicology*, **210**, 223–233.

Tamai, I., Nezu, J., Uchino, H., Sai, Y., Oku, A., Shimane, M. & Tsuji, A. (2000) Molecular identification and characterization of novel members of the human organic anion transporter (OATP) family. *Biochem. Biophys. Res. Commun.*, **273**, 251–260.

Tamiji, J. & Crawford, D.A. (2010a) The neurobiology of lipid metabolism in autism spectrum disorders. *Neuro-Signals*, **18**, 98–112.

Tamiji, J. & Crawford, D.A. (2010b) Misoprostol elevates intracellular calcium in Neuro-2a cells via protein kinase A. *Biochem. Biophys. Res. Commun.*, **399**, 565–570.

Tanabe, N., Kimoto, T. & Kawato, S. (2006) Rapid Ca(2+) signaling induced by Bisphenol A in cultured rat hippocampal neurons. *Neuro Endocrinol. Lett.*, **27**, 97–104.
Tannahill, D., Harris, L.W. & Keynes, R. (2005) Role of morphogens in brain growth. *J. Neurobiol.*, **64**, 367–375.
Taogoshi, T., Nomura, A., Murakami, T., Nagai, J. & Takano, M. (2005) Transport of prostaglandin E1 across the blood-brain barrier in rats. *J. Pharm. Pharmacol.*, **57**, 61–66.
Tarling, E.J., de Aguiar Vallim, T.Q. & Edwards, P.A. (2013) Role of ABC transporters in lipid transport and human disease. *Trends Endocrinol. Metab.*, **24**, 342–350.
Testa, C., Nuti, F., Hayek, J., De Felice, C., Chelli, M., Rovero, P., Latini, G. & Papini, A.M. (2012) Di-(2-ethylhexyl) phthalate and autism spectrum disorders. *ASN Neuro*, **4**, 223–229.
Tian, Q., Zhang, J., Chan, E., Duan, W. & Zhou, S. (2005) Multidrug resistance proteins (MRPs) and implication in drug development. *Drug Dev. Res.*, **64**, 1–18.
Tien, A.C., Tsai, H.H., Molofsky, A.V., McMahon, M., Foo, L.C., Kaul, A., Dougherty, J.D., Heintz, N., Gutmann, D.H., Barres, B.A. & Rowitch, D.H. (2012) Regulated temporal-spatial astrocyte precursor cell proliferation involves BRAF signalling in mammalian spinal cord. *Development*, **139**, 2477–2487.
Tordjman, S., Somogyi, E., Coulon, N., Kermarrec, S., Cohen, D., Bronsard, G., Bonnot, O., Weismann-Arcache, C., Botbol, M., Lauth, B., Ginchat, V., Roubertoux, P., Barburoth, M., Kovess, V., Geoffray, M.M. & Xavier, J. (2014) Gene x Environment interactions in autism spectrum disorders: role of epigenetic mechanisms. *Front. Psychiat.*, **5**, 53.
Toris, C.B., Gabelt, B.T. & Kaufman, P.L. (2008) Update on the mechanism of action of topical prostaglandins for intraocular pressure reduction. *Surv. Ophthalmol.*, **53**(Suppl 1), S107–120.
Tuchman, R. (2003) Autism. *Neurol. Clin.*, **21**, 915–932, viii.
Uauy, R. & Dangour, A. (2006) Dietary lipids and the brain during development and ageing. *Scand. J. Food Nutr.*, **50**, 27–32.
Ugele, B., St-Pierre, M.V., Pihusch, M., Bahn, A. & Hantschmann, P. (2003) Characterization and identification of steroid sulfate transporters of human placenta. *Am. J. Physiol. Endocrinol. Metab.*, **284**, E390–398.
US Environmental Protection Agency (EPA) (2013a) Health Effects Notebook for Hazardous Air Pollutants - Technology Transfer Network Air Toxics Web site. [Internet] Available from: http://www.epa.gov/ttnatw01/hlthef/hapindex.html.
US Environmental Protection Agency (EPA) (2013b) Pesticides: Regulating Pesticides - Pyrethroids and Pyrethrins. [Internet] Available from: http://www.epa.gov/oppsrrd1/reevaluation/pyrethroids-pyrethrins.html.
US Environmental Protection Agency (EPA) (2015) Integrated Risk Information System (IRIS). [Internet] Available from: http://www.epa.gov/iris/.
Vahakangas, K. & Myllynen, P. (2009) Drug transporters in the human blood-placental barrier. *Br. J. Pharmacol.*, **158**, 665–678.
Valko, M., Morris, H. & Cronin, M.T. (2005) Metals, toxicity and oxidative stress. *Curr. Med. Chem.*, **12**, 1161–1208.
Virgintino, D., Errede, M., Girolamo, F., Capobianco, C., Robertson, D., Vimercati, A., Serio, G., Di Benedetto, A., Yonekawa, Y., Frei, K. & Roncali, L. (2008) Fetal blood-brain barrier P-glycoprotein contributes to brain protection during human development. *J. Neuropathol. Exp. Neurol.*, **67**, 50–61.
Volk, H.E., Kerin, T., Lurmann, F., Hertz-Picciotto, I., McConnell, R. & Campbell, D.B. (2014) Autism spectrum disorder: interaction of air pollution with the MET receptor tyrosine kinase gene. *Epidemiology*, **25**, 44–47.
Volkel, W., Colnot, T., Csanady, G.A., Filser, J.G. & Dekant, W. (2002) Metabolism and kinetics of bisphenol a in humans at low doses following oral administration. *Chem. Res. Toxicol.*, **15**, 1281–1287.
Volpe, J. (1995) Neural proliferation, migration, organization, and myelination. In Volpe, J. (Ed.), *Neurology of the Newborn*. WB Saunders, Philadelphia, p. 43.
vom Saal, F.S. & Hughes, C. (2005) An extensive new literature concerning low-dose effects of bisphenol A shows the need for a new risk assessment. *Environ. Health Persp.*, **113**, 926–933.
de Vries, H.E., Blom-Roosemalen, M.C., van Oosten, M., de Boer, A.G., van Berkel, T.J., Breimer, D.D. & Kuiper, J. (1996) The influence of cytokines on the integrity of the blood-brain barrier in vitro. *J. Neuroimmunol.*, **64**, 37–43.
de Vries, H.E., Kuiper, J., de Boer, A.G., Van Berkel, T.J. & Breimer, D.D. (1997) The blood-brain barrier in neuroinflammatory diseases. *Pharmacol. Rev.*, **49**, 143–155.
Wang, B. & Du, Y. (2013) Cadmium and its neurotoxic effects. *Oxidative Med. Cell. Longevity*, **2013**, 898034.
Wang, L., Reiterer, G., Toborek, M. & Hennig, B. (2008) Changing ratios of omega-6 to omega-3 fatty acids can differentially modulate polychlorinated biphenyl toxicity in endothelial cells. *Chem. Biol. Interact.*, **172**, 27–38.
Wang, X., Shang, L., Wang, J., Wu, N. & Wang, S. (2010) Effect of phthalate esters on the secretion of prostaglandins (F2alpha and E2) and oxytocin in cultured bovine ovarian and endometrial cells. *Domest. Anim. Endocrinol.*, **39**, 131–136.
Wayman, G.A., Bose, D.D., Yang, D., Lesiak, A., Bruun, D., Impey, S., Ledoux, V., Pessah, I.N. & Lein, P.J. (2012) PCB-95 modulates the calcium-dependent signaling pathway responsible for activity-dependent dendritic growth. *Environ. Health Persp.*, **120**, 1003–1009.
Weiss, B. (2000) Vulnerability of children and the developing brain to neurotoxic hazards. *Environ. Health Persp.*, **108**(Suppl 3), 375–381.
Welshons, W.V., Thayer, K.A., Judy, B.M., Taylor, J.A., Curran, E.M. & vom Saal, F.S. (2003) Large effects from small exposures. I. Mechanisms for endocrine-disrupting chemicals with estrogenic activity. *Environ. Health Persp.*, **111**, 994–1006.
Williams, M.K., Rundle, A., Holmes, D., Reyes, M., Hoepner, L.A., Barr, D.B., Camann, D.E., Perera, F.P. & Whyatt, R.M. (2008) Changes in pest infestation levels, self-reported pesticide use, and permethrin exposure during pregnancy after the 2000-2001 U.S. Environmental Protection Agency restriction of organophosphates. *Environ. Health Persp.*, **116**, 1681–1688.
Windham, G.C., Zhang, L., Gunier, R., Croen, L.A. & Grether, J.K. (2006) Autism spectrum disorders in relation to distribution of hazardous air pollutants in the san francisco bay area. *Environ. Health Persp.*, **114**, 1438–1444.
Witorsch, R.J. & Thomas, J.A. (2010) Personal care products and endocrine disruption: a critical review of the literature. *Crit. Rev. Toxicol.*, **40**(Suppl 3), 1–30.
Wolstenholme, J.T., Edwards, M., Shetty, S.R., Gatewood, J.D., Taylor, J.A., Rissman, E.F. & Connelly, J.J. (2012) Gestational exposure to bisphenol a produces transgenerational changes in behaviors and gene expression. *Endocrinology*, **153**, 3828–3838.
Wong, C. & Crawford, D. (2014) Lipid signalling in the pathology of autism spectrum disorders. In Patel, V.B., Preedy, V.R. & Martin, C.R. (Eds), *Comprehensive Guide to Autism*. Springer, New York, pp. 1259–1283.
Wong, C.T., Ahmad, E., Li, H. & Crawford, D.A. (2014) Prostaglandin E2 alters Wnt-dependent migration and proliferation in neuroectodermal stem cells: implications for autism spectrum disorders. *Cell Commun. Signal.*, **12**, 19.
Woodruff, T.J., Zota, A.R. & Schwartz, J.M. (2011) Environmental chemicals in pregnant women in the United States: NHANES 2003-2004. *Environ. Health Persp.*, **119**, 878–885.
Wosik, K., Cayrol, R., Dodelet-Devillers, A., Berthelet, F., Bernard, M., Moumdjian, R., Bouthillier, A., Reudelhuber, T.L. & Prat, A. (2007) Angiotensin II controls occludin function and is required for blood brain barrier maintenance: relevance to multiple sclerosis. *J. Neurosci.*, **27**, 9032–9042.
Wozniak, A.L., Bulayeva, N.N. & Watson, C.S. (2005) Xenoestrogens at picomolar to nanomolar concentrations trigger membrane estrogen receptor-alpha-mediated Ca2+ fluxes and prolactin release in GH3/B6 pituitary tumor cells. *Environ. Health Persp.*, **113**, 431–439.
Wrobel, M.H., Mlynarczuk, J. & Kotwica, J. (2010) Influence of polychlorinated biphenyls and their hydroxylated metabolites on prostaglandins secretion from epithelial cells of bovine oviduct, in vitro. *Toxicology*, **270**, 85–91.
Yoshino, S., Yamaki, K., Li, X., Sai, T., Yanagisawa, R., Takano, H., Taneda, S., Hayashi, H. & Mori, Y. (2004) Prenatal exposure to bisphenol A up-regulates immune responses, including T helper 1 and T helper 2 responses, in mice. *Immunology*, **112**, 489–495.
Youn, S.I., Jin, S.H., Kim, S.H. & Lim, S. (2010) Porphyrinuria in Korean children with autism: correlation with oxidative stress. *J. Tox. Env. Health A*, **73**, 701–710.
Zhang, Y., Han, H., Elmquist, W.F. & Miller, D.W. (2000) Expression of various multidrug resistance-associated protein (MRP) homologues in brain microvessel endothelial cells. *Brain Res.*, **876**, 148–153.
Zhang, Y., Schuetz, J.D., Elmquist, W.F. & Miller, D.W. (2004) Plasma membrane localization of multidrug resistance-associated protein homologs in brain capillary endothelial cells. *J. Pharmacol. Exp. Ther.*, **311**, 449–455.
Zonta, M., Angulo, M.C., Gobbo, S., Rosengarten, B., Hossmann, K.A., Pozzan, T. & Carmignoto, G. (2003) Neuron-to-astrocyte signaling is central to the dynamic control of brain microcirculation. *Nat. Neurosci.*, **6**, 43–50.