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

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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 (PGE2) is released from phospholipids of cell membranes, and is important in brain development and function; PGE2 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 PGE2 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 PGE2 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, 2014). 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; Frazer 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; Silip 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
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 until birth through 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 (PGE2) are key molecules important in the development and function of the human brain (Uauy & Dangour, 2006; Innis, 2007; Carlson, 2009). PGE2 is one of the major lipid metabolites released from phospholipid membranes through the action of phospholipase A2 and cyclooxygenase (COX) enzyme activity. PGE2 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 PGE2 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 PGE2 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.
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...
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, 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).

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.

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 (Syne 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 (Syne 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...
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 & Mlynynek, 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, PGE_2, 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 & Burkhardt, 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., 2013).

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**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.
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<th>Transporter</th>
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<tr>
<td>OATP1A2 (SLCO1A2/OATP-A)</td>
<td>Localization: luminal membrane of brain capillary endothelial cells</td>
<td>Geier and Geier (2007), Gabbianelli et al. (2009), Geier et al. (2009)</td>
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<td>Substrates: PGE2, bile salts, organic anions and cations, cholate, taurocholate, glycocholate, estriol-17-glucuronide, estrone-3-sulfate, DHEAS, triiodothyronine, thyroxine, statins, unoprostone metabolite, opioid peptides</td>
<td>Hamilton et al. (2001), Garbett et al. (2008), Evans (2009), Gabbianelli et al. (2009), Hallmayer et al. (2011)</td>
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<td>Substrates: Eicosanoids, PGE2, PGD2, PGE1, PGF2α, thromboxane B2, latanoprost acid, PGH2</td>
<td>Garbett et al. (2008), Gabbianelli et al. (2009), Hartz and Bauer (2011)</td>
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<td>Substrates: PGE2, dehydroepiandrosterone, bromosulfophthalein, taurocholate, estriol-3-sulfate, DHEAS, tyroxine, bromosulfophthalein, statins, latanoprost acid, pregnolone sulfate, unoprostone metabolite</td>
<td>Hashimoto et al. (1995), Garbett et al. (2008), Gabbianelli et al. (2009)</td>
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<td>Substrates: PGE2, PGE1, PGF2α, arachidonate, estriol-3-sulfate, tyroxine, vasopressin</td>
<td>Grandjean &amp; Landrigan (2006), Grube et al. (2006), Gabbianelli et al. (2009)</td>
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<td>Developmental emergence: 7–9 weeks gestation (human fetal cerebral cortex)</td>
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<td>Substrates: PGE2, taurocholate, estriol-17-glucuronide, estriol-3-sulfate, triiodothyronine, thyroxine, unoprostone metabolite</td>
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<td>Organic anion transporters (OATs)</td>
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<td>OAT1 (SLC22A6)</td>
<td>Localization: neurons</td>
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<td>Developmental emergence: E15 (rat) and E12 (mouse)</td>
<td>Howdeshell et al. (2003), Hawkins et al. (2006)</td>
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<td></td>
<td>Substrates: PGE2, PGF2α, medium chain fatty acids, cyclic AMP and GMP, dicarboxylates, a-ketoglutarate, citrulline, urate, hydroxycinnamic acids, statins, l-lactam antibiotics, diuretic drugs, antiviral drugs, H2 receptor antagonists, NSAIDs (acetylsalicylate, ketoprofen, ibuprofen, indomethacin), nephrotoxin</td>
<td>Heudorf et al. (2007), Hertz-Picciotto et al. (2008), Hertz-Picciotto and Dehiche (2009), Hallmayer et al. (2011)</td>
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<td>Transporter</td>
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<td>OAT3 (SLC22A8)</td>
<td>Localization: abluminal membrane of brain capillary endothelial cells&lt;br&gt;Developmental emergence: E15 (rat), E14 (mouse), peak at E14–E16 (mouse)&lt;br&gt;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, NSAIDs (acetylsalicylate, ketoprofen, ibuprofen, indomethacin), toxins (ochratoxin A, perfluorooctanoic acid, aflatoxin B1), pesticides (2,4-D-dichlorophenoxyacetic)</td>
<td>Howdeshell et al. (2003), Hawkins et al. (2006), Hertz-Picciotto and Delwiche (2009), Goines and Ashwood (2013), Howdeshell et al. (2003), Hawkins et al. (2006), Hamilton et al. (2001), Hagembush 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)</td>
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<td>ABC B family transporters (ABCB-)/P-glycoprotein (P-gp)</td>
<td>ABCB1/P-glycoprotein (P-gp)&lt;br&gt;Localization: luminal and abluminal membrane of brain capillary endothelial cells, microglia, pericytes&lt;br&gt;Developmental emergence: E10.5 (mouse), E13 (rat), 10–12 weeks gestation (human)&lt;br&gt;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</td>
<td>Johnson-Restrepo et al. (2005), Dallas et al. (2006), Carlson (2009), Evans (2009), Jolous-Jamshidi et al. (2010), Hallmayer et al. (2011), Kang et al. (2003), Kalkbrenner et al. (2010), Jomova and Valko (2011), Jurewicz et al. (2013), Hamilton et al. (2001), Johnson-Restrepo et al. (2005), Hertz-Picciotto et al. (2008), Evans (2009), Frazier et al. (2014)</td>
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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 homoeostasis, 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 (Bhattacherjee et al., 2012; Aye & Keelan, 2013; Fig. 1). Substrates of ABCA1 include cholesterol, phospholipids and vitamin E (Bhattacherjee 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; Berezowska et al., 2004; Kusuhara & Sugiyama, 2005; Dallas et al., 2006; Vahakangas & Myllynen, 2009; Bhattacherjee 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; Berezowska et al., 2004; Leggas et al., 2004; Nies et al., 2004; Kusuhara & Sugiyama, 2005; Vahakangas & Myllynen, 2009; Aye & Keelan, 2013; Fig. 1). MRP2 or canicular 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 PGE2 signaling pathway can be affected in the fetal brain during critical stages of development. Abnormal PGE2 signaling in the prenatal brain may result from changes in the maternal PGE2 level due to deficient dietary supplementation, increased exposure to drugs, oxidative stress, infections and inflammation (Tamji & Crawford, 2010a,b; Wong & Crawford, 2014). Maternal PGE2 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 PGE2 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 Environmental 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 be involved in oxidative stress, 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 barrier 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 PGE2 pathway during early brain development is summarized. Moreover, it is revealed how air pollutants, pesticides and toxins in consumer products may indirectly affect the PGE2 pathway by elevating levels of inflammation, increasing levels of oxidative stress and acting as EEDCs that can affect PGE2 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-Garcidueñas et al., 2007, 2014; Moller et al., 2014). Moreover, sustained exposure could lead to DNA damage and pathologies in the brain (Calderon-Garcidueñas et al., 2007, 2014; Moller et al., 2014). In turn, inflammation is highly associated with increased levels of PGE2 (Andreasson, 2010; Nakanishi & Rosenberg, 2013). PGE2 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 (SO2) have been found to elevate PGE2 levels in macrophages (Schneider et al., 2005), lung fibroblasts (Alfar-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 (Andreasonn, 2010; Nakanishi & Rosenberg, 2013) and oxidative stress (de Vries et al., 1996, 1997) can also lead to abnormal PGE2 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 those 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 (Alabadi 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 PGE2. 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 PGE2 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 PGE2 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 PGE2 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 (Deuel 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 pyrethroids 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 (Shelton 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-Gilbert et al., 2009). Examples of OCPs include dichlorodiphenyltrichloroethane, endosulfan and dieldrin. Many OCPs are EEDCs, which mimic endogenous estrogen that can affect calcium signaling (Wozniak et al., 2005) and PGE2 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 OPPs 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 mosquitoes 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). 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). Cylfluthrin 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 PPBs) 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 PPBs) 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 become a concern for the human population. Many of these chemicals in consumer products have been shown to cross into the body and become a concern for the human population. Many of these chemicals in consumer products have been shown to cross into the body and become a concern for the human population. Many of these chemicals in consumer products have been shown to cross into the body and become a concern for the human population.

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 (Gaines & 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 PGE2 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; Gaines & 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; Crimmon, 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 (Schechter 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 (Schechter 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 PGE2, 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-
thereby in upregulating the immune response (Yoshino 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 PGE2 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 act as analogs, antagonists and EEDCs that interfere with PGE2 signaling and result in altered gene expression, 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 ethylcloprenolamine, 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, silicones and parabens are chemicals that are often found in cosmetics that have been contested as substances that put human health at risk. Silicones (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 PGE2 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 PGE2 pathway. They can act as analogs, antagonists and EEDCs that interfere with PGE2 signaling and result in altered gene expression, thereby influencing the function and development of brain cells.](image-url)
preservatives in foods such as cosmetics and pharmaceuticals, and on foods (Crinnon, 2010), and can also increase estrogenic activity (Darbre & Harvey, 2008). As mentioned earlier, elevated estrogenic activity can disturb regular PGE\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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\textsubscript{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 biphenyl; PGE\textsubscript{2}, prostaglandin E\textsubscript{2}; P-gp, P-glycoprotein; PGT, prostaglandin-transporter; PP, pyrethrin and pyrethroid; PVC, polycrylic chloride; Shh, sonic hedgehog; SLC, solute-linked carrier; TJ, tight junction.

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