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Effects of Prenatal Exposure to Endocrine Disrupters on Cerebral Cortex Development

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ABSTRACT

For several decades, the focus of most studies on endocrine disrupting chemicals (EDCs) has been the reproductive system, with fertility and hormone-dependent cancers being the most critical issues.

Cerebral cortex development is very sensitive to hormonal environment, in particular thyroid hormones and sex steroids. Experimental data concerning early exposure to polychlorinated biphenyls (PCBs) illustrate the detrimental effect of endocrine disrupters on the central nervous system. While epidemiological studies have reported a negative correlation between prenatal exposure to PCBs and cognitive performances, the molecular and cellular mechanisms of such neurotoxicity are incompletely understood. This paper will review the role of thyroid hormones and sex steroids in cerebral cortex development and will illustrate, with PCBs and bisphenol A, the potential effects of EDCs on cerebral cortex development.

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Introduction

For a long time, most studies have focused on the peripheral effects of endocrine disrupting chemicals (EDCs) on the testis and ovary (review in Diamanti-Kandarakis et al. 2009) as well as their effects on sex steroid-sensitive peripheral structures, such as the prostate or breast (Diamanti-Kandarakis et al. 2009). However, sex steroids, corticoids and thyroid hormones play a key role in the development of the central nervous system and of the cerebral cortex in particular. The critical role of these hormonal systems explains the sensitivity of the cerebral cortex to EDCs. These brain regions are complex networks of neurons and surrounding glial cells, which are modulated by paracrine or autocrine neurotransmitters as well as peripheral hormones and chemicals produced in the body or in the environment. Hormones have lifelong effects on central functions by influencing cellular proliferation, dendritic outgrowth, synaptogenesis or neurotransmitter secretion. Structural changes in the brain following hormonal alterations during fetal and perinatal life result in functional consequences in adolescence and adulthood. Typical examples are anovulation and infertility after perinatal exposure to sex steroids (Sawaki et al. 2003) and cognitive dysfunction after fetal hypothyroidism (DeLange 2000). As is the case for other systems, the developing cerebral cortex seems particularly sensitive to endocrine disruption. It is known that some neurological diseases are explained by an alteration of early processes such as progenitor proliferation, migration or differentiation. We could face a similar pattern in the case of EDCs, which could affect cortical development and lead to altered cognitive function later in life. This review will focus on the effects of EDCs on cerebral cortex development.

Developmental Processes in the Cortex Regulated by Thyroid Hormones and Sex Steroids

Knowing the developmental processes that depend on sex steroids and thyroid hormones, one can hypothesize on the stages potentially affected by EDCs. We will review here the multiple actions of thyroid hormones and sex steroids on cortical development. Estradiol is a possible factor promoting the development, function and survival of neurons (McEwen and Alves 1999) through classical genomic interactions with the nuclear estrogen receptor (ER) and also non-genomic interactions with membrane receptors. Neurons, astrocytes and neuronal progenitors express ERs. In particular, astrocytes influence neural development in part by synthesizing estrogens (Garcia-Segura and Melcangi 2006). Interestingly, alpha-fetoprotein (AFP) is expressed at high levels in radial glial cells but at lower levels by intermediate progenitors. Thus high levels of AFP in the ventricular zone could inhibit E2 (17-beta Estradiol)-promoted proliferation in this region whereas low levels of AFP in the subventricular zone could allow a stronger effect of E2 on intermediate progenitors (Martinez-Cerdeno et al. 2006). Estrogens also stimulate neurogenesis in adult rodents and increase proliferation in cortical progenitor cells by shortening the G1 phase (Martinez-Cerdeno et al. 2006). Because EDCs can affect the ER directly or indirectly through estrogen

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biosynthesis or metabolism, it is important that studies of the action of EDCs examine those different structures and functions in the cortex.

During fetal and neonatal life, neuronal and glial proliferation, migration, and differentiation depend on thyroid hormones. Thyroid hormone action is mediated by two classes of nuclear receptors (Forrest and Vennstrom 2000) that exhibit differential spatial and temporal expression in the brain, suggesting that thyroid hormones have multiple functions during brain development (Horn and Heuer 2010).

Thyroid hormone receptors are expressed in neurons, astrocytes, and oligodendrocytes and precursors before the fetal thyroid is functional, suggesting a role for hormones of maternal origin. Triiodothyronine (T3) regulates the expression of genes coding for the growth factors, cell surface receptors and transcription factors involved in cell cycle regulation and proliferation (reviewed in Puzianowska-Kuznicka et al. 2006). The action of T3 is not homogeneous and depends on the cell type and its developmental state. T3 blocks proliferation and induces differentiation of oligodendrocyte progenitor cells (Baas et al. 1997). This effect results from a rapid decrease of the transcription factor E2F1 in oligodendrocyte precursors, which induces a decrease of proliferation by arresting the cells in G1 and S phases (Nygard et al. 2003). Tokumoto et al. (2001) also showed that thyroid hormones promote oligodendrocyte differentiation through another pathway involving p53 proteins. In addition to these few studies suggesting a role for thyroid hormones on cell proliferation in the cortex, several studies have reported an effect on cell migration and differentiation. For example, T4 promotes actin polymerization through non-genomic action in developing neurons (reviewed in Cheng et al. 2010). Actin polymerization is necessary to recognize the laminin guidance molecule during migration (Farwell et al. 2005). Thyroid hormones also regulate the organization of the actin cytoskeleton in astrocytes during development, thus affecting the production and deposition of laminin at the surface of astrocytes that is necessary for neuronal migration (Farwell and Dubord-Tomasetti 1999). In ex vivo studies, maternal hypothyroxinemia alters radial and tangential neuronal migration (Lavado-Autric et al. 2003; Auso et al. 2004). In these experiments, green fluorescent protein-medial ganglionic eminence (GFP-MGE)-derived neurons from hypothyroxinemic mothers showed a normal migratory behavior whereas GFP-MGE-neurons from normal or hypothyroxinemic mothers showed disrupted migration when explanted into the neocortex of embryos from hypothyroxinemic dams. These studies suggest an effect caused not by the migratory neurons themselves but by elements guiding the migration (Cuevas et al. 2005). Thyroid hormones also regulate the expression and distribution of molecules, such as actin or tenascin (Farwell et al. 2005; Alvarez-Dolado et al. 1998), that interact with the extracellular matrix and facilitate neurite outgrowth. Overall, these examples illustrate that thyroid hormones are involved in multiple aspects of early brain development including proliferation, differentiation and migration of progenitors. Disruption of thyroid function by EDCs such as PCBs could thus cause neurological deficits that are very similar to hypothyroidism.

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Epidemiological Data

As stated above, thyroid hormones and sex steroids play a fundamental role in the development of the cerebral cortex, and many environmental chemicals are able to alter thyroid function or sex steroid action. One example is a group of chemicals called polychlorinated biphenyls (PCBs), which is a family of 209 different congeners used in lubricating oils and plasticizers. Because of their long half-life (Ogura et al. 2005), they are still ubiquitous environmental contaminants, found in high concentrations in humans and animals, even though they have been banned in Europe and the USA since the 1970s. The first observation pointing to the neurotoxic effects of PCBs followed an accidental exposure in Taiwan in which children exposed in utero showed impaired cognitive function at5 years of age (McKinney and Waller 1994). The major difficulty in such studies is the long delay between the exposure and its measurable effect. Several other follow-up studies have shown a negative correlation between in utero exposure to PCBs and cognitive performance and memory in infants and children (reviewed in Schantz et al. 2003). Those results are consistent with observations made in rodents. Itis interesting to note that the levels of exposure in recent studies are lower than in earlier studies but still negatively correlate with cognitive function. More recent studies are developing analytic methods to correlate neurodevelopmental toxicity with specific congeners. Some PCB congeners could lower thyroid hormones levels in serum and thus induce a state similar to hypothyroidism. However, epidemiological studies reported levels of T3, T4 and thyroid-stimulating hormone (TSH) that were in the normal range in pregnant women and newborns. But some studies reported that higher levels of PCBs in maternal and cord blood were associated with higher levels of TSH in newborns.

Bisphenol A (BPA) is a ubiquitous industrial chemical used in the manufacture of plastics and epoxy resins. It is present in many plastic bottles, baby bottles and food cans and is found in the urine of more than 90% of Americans (Melzer et al. 2010). Fetuses and newborns seem to be particularly exposed since BPA is known to cross the placenta and is found in high concentration in amniotic fluids and cord serum (Sch€onfelder et al. 2002). BPA is a weak estrogenic compound binding to ERa and b as well as membrane receptors. It also antagonizes T3 activation of the thyroid receptor, and developmental exposure to BPA induces a state similar to thyroid hormone resistance. Very little data are available concerning the effects of BPA on cerebral function in human. One caveat for those studies is that virtually everybody in the Western world has been exposed to BPA. However, knowing that BPA alters sex steroid and thyroid hormone function, one can hypothesize that perinatal exposure to BPA could lead to alterations in cerebral cortex development. Nakagami et al. (2009) reported an alteration in male behavior toward mothers after prenatal exposure to BPA in non-human primates, which suggests that, because of its interaction with sex steroid receptors, BPA could alter the sexual differentiation of the brain taking place perinatally.

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Molecular Mechanisms of Endocrine Disruption of Cerebral Cortex Development

The molecular mechanisms by which EDCs can cause alterations of cerebral cortex development are still incompletely understood, but some data are available for PCBs. Some studies suggest that PCBs cause a state of relative hypothyroidism that could explain their neurotoxicity. Interestingly, the cerebellum and the auditory system that depend on thyroid hormone are very sensitive to PCBs (Koibuchi and Chin 2000). However, PCBs do not only produce effects consistent with hypothyroidism, since the expressions of some thyroid hormone-responsive genes are increased after neonatal exposure to PCBs (Gauger et al. 2004). Some in vitro studies have shown that some PCBs congeners act as thyroid hormone receptors agonists (Fritsche et al. 2005). Based on their chemical structure, PCBs can act through different pathways (McKinney and Waller 1994). Coplanar congeners bind to cytosolic aryl hydrocarbon receptors (AhR), a ligand-dependent transcription factor involved in cell proliferation and differentiation (Dietrich and Kaina 2010). However, the neurotoxic effects of PCBs on development might not be entirely explained by AhR. Some PCBs can also alter neurotransmission and intracellular signaling (Kodavanti 2006).

BPA is another example of the complexity of the mechanisms of action of EDCs on the brain. Some studies suggest that BPA could indeed affect cerebral cortex development. Prenatal exposure to BPA does not affect progenitor cell proliferation in mice but it alters the number of cells in each of the cortical layers postnatally (Nakamura et al. 2007). It has also been shown that BPA could have an antiestrogenic action on synaptogenesis in the rodent and non-human primate hippocampus (Hajszan and Leranth 2010; Leranth et al. 2008). BPA is classically known to act as an estrogen agonist with an affinity for ERs that is much lower than estradiol. It is also able to interact with membrane receptors at very low doses. Besides its action on the ER, BPA can also act as a competitive inhibitor for androgen receptors and can disrupt their nuclear localization as well as their trans-activation (review in Wolstenholme et al. 2010). Those actions at the level of the sex steroids receptors could alter the estrogenic/androgenic balance existing in the fetal brain and explain a possible disruption of sexual differentiation of the cerebral cortex. Besides its action on sex steroid receptor, BPA appears to act as a thyroid hormone receptor antagonist in vitro. It blocks T3-dependent oligodendrocyte development (Seiwa et al. 2004) and induces a state similar to thyroid hormone resistance in vivo with increased T4 but did not change THS in exposed animals (Zoeller et al. 2005). Some new mechanisms of action for BPA have been described in the brain. It has recently been shown that low doses of BPA prenatally increase AhR (Nishizawa et al. 2005a) and AhR (Nishizawa et al. 2005b) repressor expression in the brain, suggesting that BPA could affect the cell proliferation and differentiation regulated by AhR. Very recently, perinatal exposure to BPA has been shown to alter methylation of genes involved in prostate cancer (Ho et al. 2006) as well as genes coding for fur color (Dolinoy et al. 2007). But only one study focused on the methylation status of the brain after exposure to BPA. Prenatal exposure to low doses of BPA induced a decreased methylation of two loci, VPS52 and LOC72325, in the brain that correlated with an increased expression of those genes (Yaoi et al. 2008). The function of those genes is not completely understood but the authors

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hypothesize that changes in their methylation could promote neuronal differentiation and migration.

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