Hormonal Regulation of Cerebellar Development and Its Disorders

Noriyuki Koibuchi

Abstract Cerebellar development and plasticity involves in various epigenetic processes that activate specific genes at different time points. Such epigenetic influences include hormonal signals from endocrine cells. Various hormone receptors are expressed in the cerebellum, and cerebellar function is greatly influenced by hormonal status. The aim of this chapter is to introduce several key features of hormones and their receptors involved in the regulation of cerebellar development and plasticity. Furthermore, cerebellar developmental disorders caused by aberrant hormonal status are also discussed. This chapter also covers the effect of endocrine-disrupting chemicals that may alter hormone functions in the cerebellum.

Keywords Steroid hormone • Thyroid hormone • Nuclear receptor • Critical period • Endocrine-disrupting chemicals

Hormone and Cerebellar Development: A General Overview

To understand the functional organization of the central nervous system (CNS), including the cerebellum, it is important to consider the process by which neurons differentiate to establish their role and interact with specific target cells to form functional pathways. The development of the brain involves epigenetic processes that activate specific genes during different time frames. As shown in Fig. 1, epigenetic influences that regulate brain development may originate from the neuronal cell itself or from outside of the CNS. The former includes spatial and temporal pattern of intrinsic gene expression tightly regulated by their molecular programs. The latter includes sensory inputs, mediated by the peripheral nervous system and hormonal influence from endocrine cells. These are also crucial stimuli for brain development. Environmental influences, such as stressors, endocrine-disrupting chemicals (EDCs), and undernutrition may affect such processes.

N. Koibuchi (✉)
Department of Integrative Physiology, Gunma University Graduate School of Medicine, 3-39-22 Showa-machi, Maebashi, Gunma 371-8511, Japan
e-mail: nkoibuch@med.gunma-u.ac.jp

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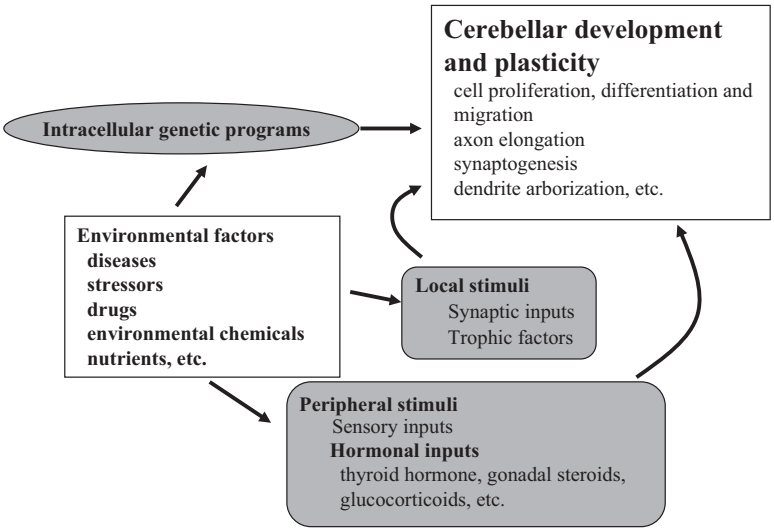

Fig. 1 Schematic diagram showing genetic and epigenetic influences and its modulation by environmental factors involved in cerebellar development and plasticity

The cerebellar cortex forms well-organized structures involving a highly specific and uniform arrangement of cells and microcircuitry [1]. The cerebellum is one of the few sites in the CNS where the pattern of intrinsic connections is known in considerable detail. These features make the cerebellum an ideal system to study the mechanisms of neural development and plasticity. Based on such advantages, many excellent works have been done at various levels ranging from basic science to clinical disorders. In contrast, although a number of hormone receptors are expressed in the cerebellum, and cerebellar function is greatly influenced by hormonal status, a relatively smaller number of studies have evaluated the role of hormonal signaling on development and plasticity of the cerebellum.

Among circulating hormones, a group of small lipophilic hormones such as steroids (corticosteroids, progesterone, androgens, and estrogens) and thyroid hormone (TH) may particularly play an important role in mediating environmental influences. Because of their chemical nature, these are able to cross the blood-brain barrier (BBB) more easily than peptide hormones, although the existence of specific transporters has been proposed [2]. Receptors for such lipophilic hormones are mainly located in the cell nucleus (nuclear receptor, NR) and represent the largest family of ligand-regulated transcription factors [3]. As shown in Fig. 2, the molecular structure of the NR superfamily is homologous. It consists of a highly variable N-terminal domain, which contains a transactivation domain (activation function-1, AF-1), DNA-binding domain (DBD), and ligand-binding domain (LBD). The DBD is the most homologous among these domains. The LBD, which also shares certain homology among NRs, is also responsible for dimerization of NRs and ligand-dependent transactivation (activation function-2, AF-2). To activate or repress the

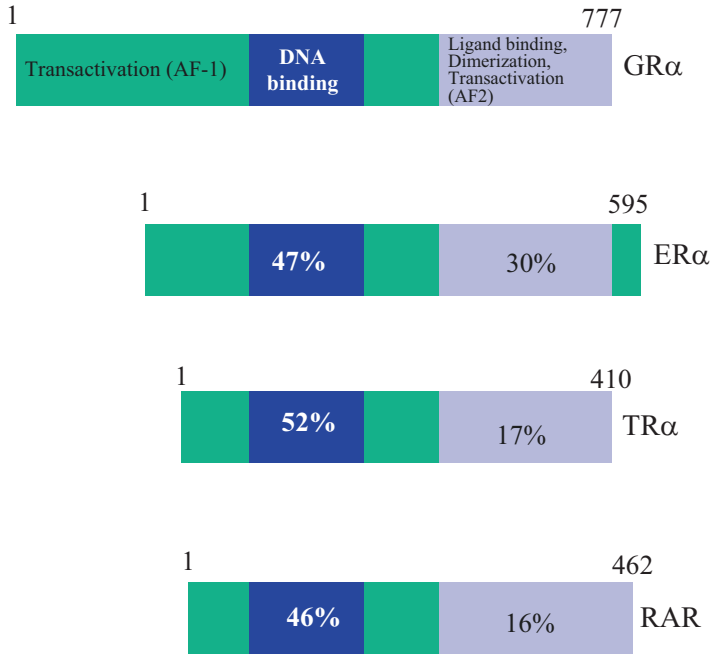

Fig. 2 Protein sequence homology among representative nuclear hormone receptors. *ERα* estrogen receptor alpha, *GRα* glucocorticoid receptor alpha, *RAR* retinoic acid receptor, *TRα* thyroid hormone receptor alpha. Numbers indicate amino acid number

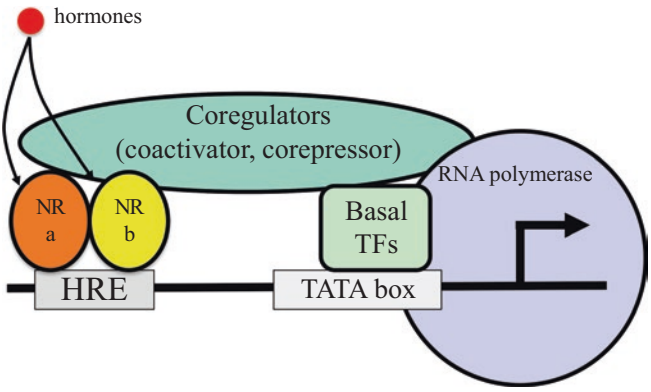

Fig. 3 Interactions of nuclear receptor (*NR*), transcriptional coregulators, and basal transcriptional machinery such as basal transcription factors (*TFs*). NRs bind to hormone response element (*HRE*) located in the promoter region of target genes

transcription of target gene, NRs bind to a specific nucleotide sequence called the hormone response element (HRE) located in the promoter region of target genes (Fig.3). Then NRs recruit a variety of coregulators in a ligand-dependent manner, such as coactivator and corepressor complexes, which then modulate chromatin

structures [4]. With a specific pattern of expression, the NRs are widely distributed in the CNS, as well as in other organs [5]. In the cerebellum, NRs are expressed in a specific temporal and spatial pattern [6]. However, the role of these NRs on cerebellar development and function is not fully understood.

Among the lipophilic hormones, involvement of TH (triiodothyronine [T_3] and thyroxine [T_4]) on cerebellar development has been well studied. Deficiency of TH during the postnatal development results in abnormal cerebellar morphogenesis in rodents [7–9] and humans [10]. Conversely, although the importance of gonadal steroids such as estrogen, progesterone, and testosterone on the development and functional maintenance of the CNS has been well documented, the cerebellum is considered to be relatively insensitive to gonadal steroids. However, recent studies have clarified that gonadal steroids play an important role in cerebellar development and may be involved in various health and disease states [11]. In addition to the supply from circulation, these gonadal steroids are produced locally within the Purkinje cells [12]. Corticosteroids, particularly glucocorticoid, are crucial for the maturation of various organ systems, including the brain [13]. Furthermore, since recent studies have shown the critical role of the cerebellum on social, cognitive, and emotional behaviors [14]; other studies on the role of glucocorticoids on cerebellar development are currently underway. Additionally, it should be noted that these thyroid/steroid hormone-mediated pathways can be disrupted by prescription drugs and environmental chemicals [15].

This chapter will provide useful information regarding the hormonal regulation of cerebellar development and plasticity. Furthermore, cerebellar developmental disorders caused by aberrant hormonal status are also discussed.

Cerebellar Disorders Induced by Aberrant TH Systems

The importance of T_3 and T_4 in brain development has been well documented [7–9]. Deficiency of THs during fetal and early postnatal period results in severe mental retardation. In humans, this is known as cretinism [10]. In the 1980s when newborn screening was introduced in many countries, the initial prevalence of cretinism was 1/3,000–1/4,000 births worldwide; however, recent studies have shown that the prevalence has increased to 1/1,400–1/2,800. This increase may be attributed to the change in diagnostic strategy from serum T_4 measurement to thyrotropin (TSH) measurement, allowing the identification of milder cases. If the diagnosis of cretinism is delayed, the risk of mental retardation and neurologic sequelae, such as poor motor coordination, ataxia, spastic diplegia, muscular hypotonia, strabismus, learning disability, and diminished attention span, is likely to increase.

T_4 enters the brain through the BBB more easily than T_3, an active form of TH [16]. After crossing the BBB, T_4 is taken up by astrocytes and deiodinated to produce T_3 by type 2 iodothyronine deiodinase [17]. T_3 is then transferred to neurons or oligodendrocytes, possibly via monocarboxylate transporter 8 (MCT8) [18]. The effects of THs are mainly exerted through the nuclear TH receptor (TR). At least three TR isoforms are expressed in the CNS (TRα1, TRβ1, and TRβ2) [19].

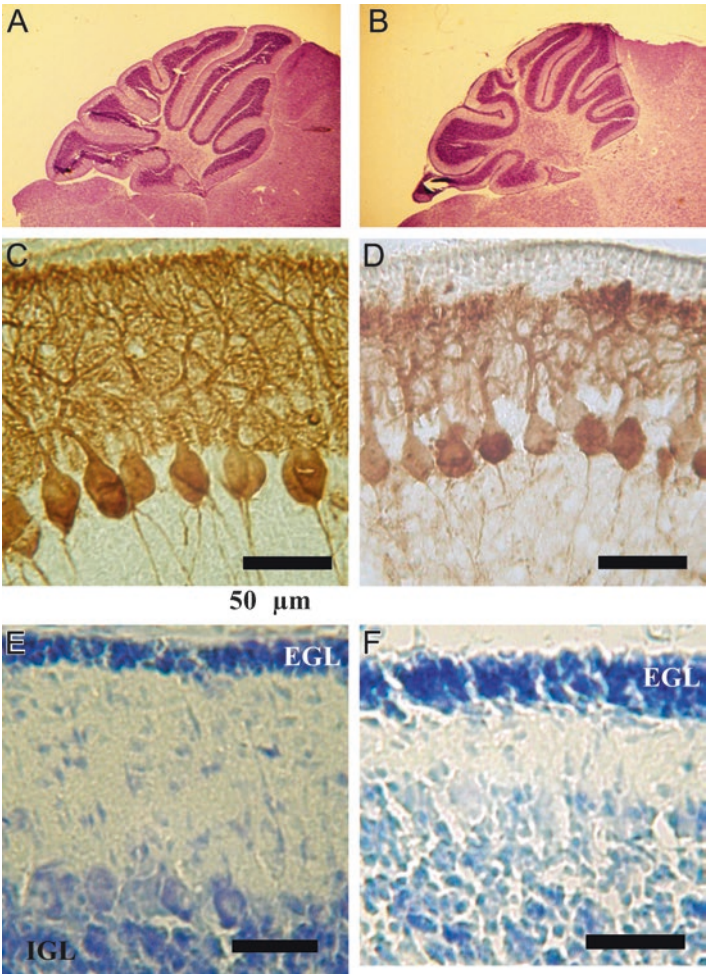

Fig. 4 Effect of congenital hypothyroidism in rat model. Rdw congenital hypothyroid rat, which harbors mutated thyroglobulin gene, shows delayed cerebellar development (**b**, **d**, **f**) compared to control animal (**a**, **c**, **e**). Note the decrease in dendrite arborization of Purkinje cell (**d**) and delayed disappearance of the external granule cell layer (EGL) (**f**)

Perinatal hypothyroidism dramatically affects cerebellar morphogenesis and function. In an animal model of perinatal hypothyroidism, the growth, dendritic arborization, and dendritic spines of Purkinje cells are all markedly decreased. Synaptogenesis between Purkinje cells and parallel fibers is dramatically repressed. The disappearance of the external granule cell layer is postponed as a result of the delayed proliferation and migration of the granule cells into the internal granule cell layer (Fig. 4) [7–9]. TRs are expressed in most subsets of cells in the developing cerebellum in both rodents and humans [20, 21]. TRα1 is abundant in granule cells, whereas TRβ1 is mainly expressed in Purkinje cells. In perinatal hypothyroidism,

the expression of many cerebellar genes is altered [8]. Representative TH-responsive genes in the cerebellum include neurotrophins such as nerve growth factor, BDNF, NT3, and NT4/5, and receptors such as the inositol triphosphate 3 receptors, and retinoic acid receptor-related orphan receptor α, hairless, and myelin basic protein genes. The THs regulate the expression of many of these genes only during a limited period of development. Various animal models harboring TR mutation have been used to study the role of TR in cerebellar development [22]. Interestingly, TRα knockout mice, TRβ knockout mice, and TRα/TRβ double knockout mice do not display obvious cerebellar defects, suggesting that most of the consequences of congenital hypothyroidism in the brain are caused by the detrimental activity of unliganded TR. In fact, in animal models expressing dominant-negative TR, which cannot bind to TH, cerebellar phenotypes, such as disrupted motor coordination, are evident [23–26], suggesting that unliganded TR may cause aberrant phenotypes. In human cases of resistance to TH (RTH) caused by mutation of TR genes, the clinical phenotype is highly variable [27, 28]. This probably depends on the severity of the mutation. However, abnormal motor coordination, which is always evident in animal models, is not common in human cases. Their representative neurological symptoms are emotional disturbances and hyperkinetic behavior [27]. Although the involvement of the cerebellum on such behavioral alterations is also known as cerebellar cognitive affective syndrome [29], further study is required to clarify such phenotypic differences among species.

In addition to cretinism and RTH, recent studies have shown another congenital disease induced by aberrant TH system. Another human disorder related to the TH system is Allan-Herndon-Dudley syndrome, which is an X chromosome-linked disease. The symptoms are hypotonia, dysarthria, athetoid, or other distal limb movements, muscle hypoplasia, and severe mental retardation [30]. Linkage studies have identified the gene locus in Xq 13.2. This region encodes for MCT8 that transports T_3 into the neurons [31]. Animal studies have shown the disruption of cerebellar development by knocking down MCT8 in the Purkinje cells [32]. Although MCT8 is responsible for the TH transport into neurons, the phenotype of Allan-Herndon-Dudley syndrome is much more severe than that in a patient with cretinism or RTH. Thus, further study is necessary to clarify whether this syndrome is induced only by disrupted TH transport or by other additional factors.

Cerebellar Disorders and Gonadal Steroids

Although the importance of gonadal steroids, such as estrogen, progesterone, and testosterone in the development and functional maintenance of the brain, has been well documented, the cerebellum has been previously considered relatively insensitive to gonadal steroids. However, recent studies have clarified that gonadal steroids play an important role in cerebellar development and may be involved in various health and disease states [11]. Aside from the supply from circulation, these gonadal steroids are also produced locally within the Purkinje cells [12].

Testosterone and estradiol (E2) are the two major gonadal steroids synthesized in the testes and the ovaries, respectively. During brain development, gonadal steroids regulate the formation of structures of many brain regions. In late embryonic period, the testes in males start producing testosterone. Because of their lipophilic nature, steroids can pass across the BBB by simple diffusion [33]. Testosterone is then converted to E2 by an aromatase. In contrast, ovaries in females differentiate much later during development and do not secrete E2 during this period. Thus, during the perinatal critical period, there are significantly higher levels of E2 in males compared to females. These are thought to act on male brain development [34]. E2 regulates apoptosis to produce sexually dimorphic cell numbers, dendritic spine formation, neuronal migration, and synaptic organization in the hypothalamic regions, most of which are key regions for regulating male- and female-sexual functions in the adult brain. Because of the lack of estrogen exposure during the perinatal period, the female brain is thought to develop without involvement of E2. However, studies of aromatase gene using knockout mice have suggested that E2 produced by the ovaries during a prepubertal period plays a role in the differentiation of the female-typical brain [35].

In addition to estrogen, androgens, particularly testosterone, directly acting on the androgen receptor (AR), are also thought to play a role in brain masculinization. This is based on studies of human patients with complete androgen insensitivity syndrome and on patients with mutations in the aromatase gene, as well as on studies of rodents with the testicular feminization mutation, which produces a nonfunctional AR [36].

Gonadal steroids also play an important role in the development of the cerebellum. Two nuclear estrogen receptors (ERα and ERβ) were detected in an immature cerebellar granule cell line derived from late embryonic mouse cerebellum [37]. Quantitative reverse transcription-polymerase chain reaction (RT-PCR) studies have shown that both receptors are expressed in the cerebellum from birth to adulthood but levels of ERβ mRNA are significantly higher than those of ERα in neonatal rats [38]. Nevertheless, ERα levels are higher than those in adults during the neonatal period [38]. ERα is predominantly expressed in the Purkinje cells [39]. In contrast, the level of ERβ protein decreased transiently at P5 and P7 in rodents and then increased dramatically at P10 followed by a subsequent decrease to adult levels [40]. ERβ immunoreactivity was detected in various neurons, including Golgi, Purkinje, and basket cells, and the expression in each cell type occurs on different postnatal days. Additionally, differentiating external granular layer cells and glial cells also show ERβ immunoreactivity. Differential expression profiles of ERα and ERβ suggest that E2 exerts its actions in a cell type-specific manner via binding to the two ERs, which play distinctive roles in cerebellar development. Additionally, there may be a possibility that estrogen acts rapidly through a membrane-associated receptor in the developing cerebellum [41].

As discussed above, during the late embryonic period, E2 converted from testosterone may be major gonadal steroid that may have some effect in the developing cerebellum. Previous studies showing the expression of aromatase in mid gestation in monkey [42] and early postnatal age in rat [43] support this hypothesis. Then at

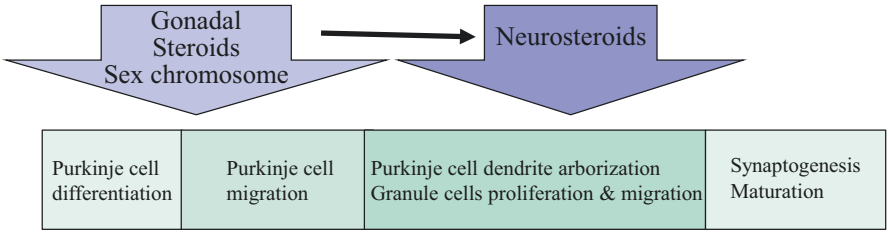

Fig. 5 Possible differential roles in gonadal steroids and neurosteroids during cerebellar development

the later stage, the estrogen level in the cerebellum increases relative to that in the plasma [44] with the expression of enzymes responsible for estrogen [43] and progesterone [45] synthesis, indicating that gonadal steroids are locally produced as "neurosteroids." The most evident action of gonadal steroid is that estrogen and progesterone promote dendritogenesis and increases dendritic spine density [44, 46]. Taken together, gonadal steroids produced in the testes or ovaries may play an important role during the early cerebellar development. Then, de novo synthesized neurosteroids may play a major role at a later stage of development. Additionally, possible sex chromosome effects have been proposed [47]. The diagram showing the influence of gonadal steroids on cerebellar development is shown in Fig. 5.

Whether there are any sex differences in cerebellar architecture remains controversial. Some magnetic resonance imaging (MRI) studies have reported that the cerebellar size in men, both adults [48] and children [49], is larger than that in women, and other MRI studies failed to detect such differences [50]. Biochemically, the levels of aromatase and several enzymes related to estrogen synthesis are higher in postnatal male rats than in females [43], whereas calbindin levels are higher in female mice [47]. While these are only few examples related to sexual differences in the cerebellum, sexual dimorphism is not evident in gene expression patterns in the cerebellum.

In spite of the fact that no clear sex differences in cerebellar morphology and gene expression were observed, there is a clear sex difference in cerebellar pathology in several developmental diseases in humans and related animal models. For example, the prevalence of autism is four times higher in men [51], and autistic patients commonly show increased cerebellar volumes during childhood and hypoplasia in adult [52, 53]. In postmortem tissue in autistic patients, Purkinje and granule cells were reported to be lower in number [54, 55]. Another clinical example is attention-deficit hyperactivity disorder (ADHD), which affects two to four times more males than females [56]. Untreated children show the decreased volume of the posterior inferior vermis [57]. In our animal model, when polychlorinated biphenyl (PCB), an environmental chemical pollutant and developmental neurotoxicant, is administered postnatally to dams, pups present ADHD phenotype [58]. Hyperactivity was more evident in males. Additionally, motor coordination was more severely disturbed in male rats (Fig. 6) [58]. More recently, the change in the volume of several cerebellar regions in transgender individuals has been reported, although the mechanisms underlying such cerebellar structural difference are unknown [59, 60]. To clarify the molecular mechanisms of sexual differences in cerebellar pathology, further study is necessary.

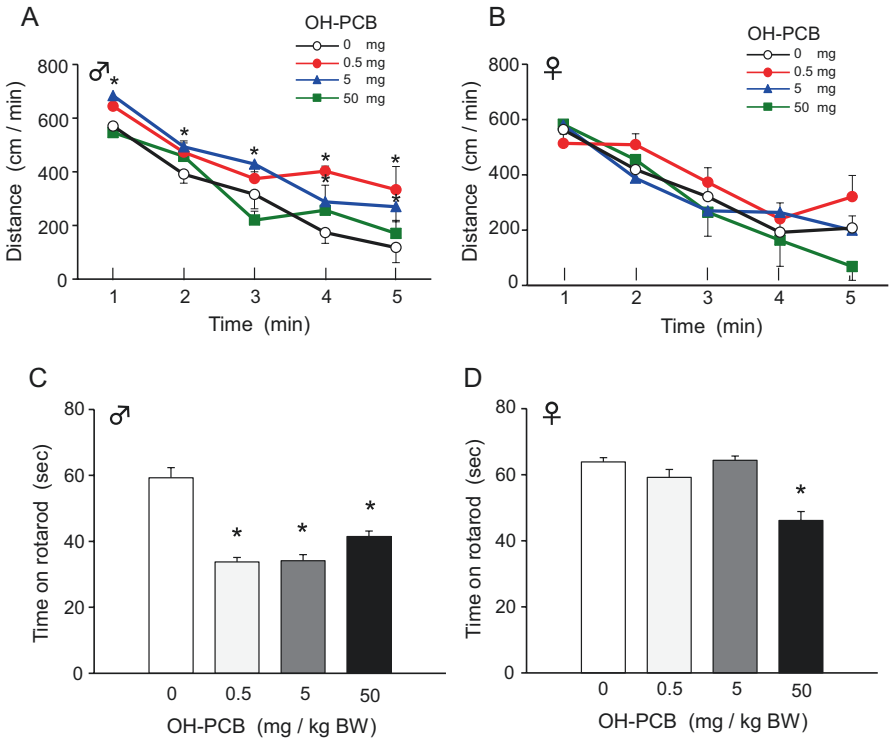

Fig. 6 Sexual difference in the effect of perinatal exposure to hydroxylated polychlorinated biphenyl (OH-PCB106). PCB was orally administered to the dam every other day from postpartum day 3–13 [58]. (**a**, **b**) Effects of PCB on locomotor activity in the open field in male (**a**) and female (**b**) rat. (**c**,**d**) Effect of PCB on motor coordination on rotarod in male (**c**) and female (**d**) rat. Note that behavioral alteration was more evident in male. $P < 0.05$ vs control (no PCB)

Cerebellar Disorders Induced by Corticosteroids

Glucocorticoids and mineralocorticoids are major adrenal steroid hormones (corticosteroids) synthesized in the adrenal cortex. Mineralocorticoids regulate sodium and potassium levels, whereas glucocorticoids are involved in the stress response and carbohydrate metabolism. Glucocorticoid levels are controlled through the hypothalamic-pituitary-adrenal (HPA) axis, whereas mineralocorticoid levels are regulated by the renin-angiotensin-aldosterone system. The effect of corticosteroids in the brain is mainly exerted through binding to intracellular receptors, the glucocorticoid receptor (GR), and mineralocorticoid receptor (MR) [61]. Although GR binds preferentially to glucocorticoids, MR can bind to both glucocorticoids and mineralocorticoids with similar affinity. The specificity of MR is determined by the colocalized expression of 11 β-hydroxysteroid dehydrogenase 2 (11β-HSD2), which inactivates cortisol [61]. Additionally, rapid effects that respond within minutes are regulated by non-genomic action [62].

In most mammalian species, the glucocorticoid concentration increases dramatically during the perinatal period, and such increases are associated with the maturation of several organs including the lungs and brain [63]. In the developing CNS, corticosteroids regulate neurogenesis, neuronal morphology, and function in response to chronic stress. During fetal rat brain development, GRs are expressed widely, including cerebellum, with high levels of 11β-HSD2 and much lesser levels of MR [64], indicating that the developing cerebellum is protected from excess glucocorticoids. In the early postnatal rat cerebellum, however, the MR expression in Purkinje cell become evident, followed by the GR expression within this cell type and MR expression in migrating granule cells, the internal granule layer, and the deep cerebellar nuclei [65]. Conversely, 11β-HSD was specifically expressed in the external granule cell layer [66], indicating that MR as well as GR may mediate postnatal glucocorticoid action in the cerebellum. Prenatal glucocorticoids influence the development of Purkinje neurons [67]. Furthermore, the glucocorticoid-binding capacity of the neonatal rat cerebellum (P8-P15) is highest among brain regions, such as the cerebral cortex, hippocampus, and olfactory bulb [68]. These results indicate that glucocorticoids play an important role in the developing cerebellum to induce multiple changes in response to various environmental stimulations.

As discussed above, studies of rodents have shown that the cerebellum has higher glucocorticoid binding capacity on P8-P15 [68], which is equivalent to the human perinatal period. Such a high sensitivity to glucocorticoid stimulation may make the cerebellum susceptible to development alterations if glucocorticoid homeostasis is disrupted by perinatal stress or glucocorticoid administration. In rats, cortisone treatment during the prenatal [69] and postnatal [70] development resulted in a decreased number of cerebellar granule cells. Such a decrease may be caused by an increased sensitivity to oxidative stress by perinatal glucocorticoid treatment, inducing cell death [71]. In humans, premature newborns suffering from respiratory distress caused by lung immaturity or mothers at a risk of premature delivery before 34 weeks of gestation are sometimes administered glucocorticoid therapy. Newborns who received such treatment sometimes show neuromotor/cognitive disorders [72], including abnormal cerebellar development [73]. Thus, careful use of glucocorticoid therapy (i.e., dose and timing) is required for fetuses and newborns.

Stressful experiences in the prenatal or early postnatal period may increase the risk of neurological and psychiatric disorders, such as ADHD, autism, schizophrenia, and depression [74]. The cerebellum is one of the major brain regions to be directly affected by stressful experience, and the involvement of glucocorticoid system has been proposed as the culprit for such abnormalities [75]. Maternal deprivation (MD) during the early postnatal period in rats causes retardation in the development of cerebellar-dependent motor coordination and behavioral abnormalities similar to those in schizophrenia [76]. In MD rat, a transient increase has been reported in several neurotrophic factors, such as brain-derived neurotrophic factor, TrkB, and oligodendrocyte-myelin glycoprotein [77]. These results support the possibility that abnormally increased levels of glucocorticoids caused by neonatal stress during development are associated with structural abnormalities in the cerebellum, leading to psychosomatic abnormalities in adulthood. However, in spite of high glucocorti-

coid binding capacity in the developing cerebellum, the role of glucocorticoid during cerebellar development has not yet been fully clarified. Further investigations, including studies with human subjects, are necessary.

Environmental Chemicals That May Disrupt Cerebellar Development Through Disruption of Hormone Actions

As discussed above, various hormones are involved in cerebellar development and disruption of such hormonal environment may affect such development. A large number of synthetic or natural chemicals may disrupt hormonal environment. These are referred to as EDCs. The exact definition of an EDC by the World Health Organization (WHO) is as follows: "An endocrine disrupting chemical is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny or (sub) populations" [78]. As many hormones have distinct effects, specifically in critical periods during development, fetal or early neonatal exposure to such chemicals may induce adverse effect in various organs, including the CNS [79]. Recent advances in EDC research have provided many important data regarding the neurotoxicity of such EDCs [80]. Table 1 shows representative EDCs that are categorized as pharmaceuticals, herbicides, fungicides, insecticides, industrial chemicals and byproducts, and organic and inorganic metals [79, 80]. Importantly, although there are approximately 1,000 EDCs, more than 100,000 chemicals exist in the environment. The

Table 1 Environmental chemicals showing hormonal or antihormonal activities

Classification	Chemicals
Pharmaceuticals	Hormones or antihormones, amiodarone, DES, fenamate, phenobarbital, phenytoin
Herbicides	2,4,-D, 2,4,5,-T, alachlor, amitrole, atrazine, linuron, metribuzin, nitrofen, trifluralin
Fungicides	Benomyl, ethylene thiourea, fenarimol, hexachlorobenzene, mancozeb, maneb, metiram – complex, tri-butyl-tin, vinclozolin, zineb
Insecticides	Aldicarb, beta-HCH, carbaryl, chlordane, chlordecone, DBCP, DDT, dicofol, dieldrin, DDT and metabolites, endosulfan, heptachlor/H-epoxide, lindane (gamma-HCH), malathion, methomyl, methoxychlor, oxychlordane, parathion, synthetic pyrethroids, transnonachlor, toxaphene
Industrial chemicals and by-products	Bisphenol – A, polycarbonates, butylhydroxyanisole (BHA), chloro- and bromo-diphenyl, dioxins, furans, nonylphenol, octylphenol, PBDEs, PCBs, pentachlorophenol, penta- to nonylphenols, perchlorate, PFOA, PFOS, p-tert-pentylphenol, phthalates, styrene
Metals	Cadmium, gadolinium, lead, manganese, methyl-mercury, organic-tins (e.g., TBT)

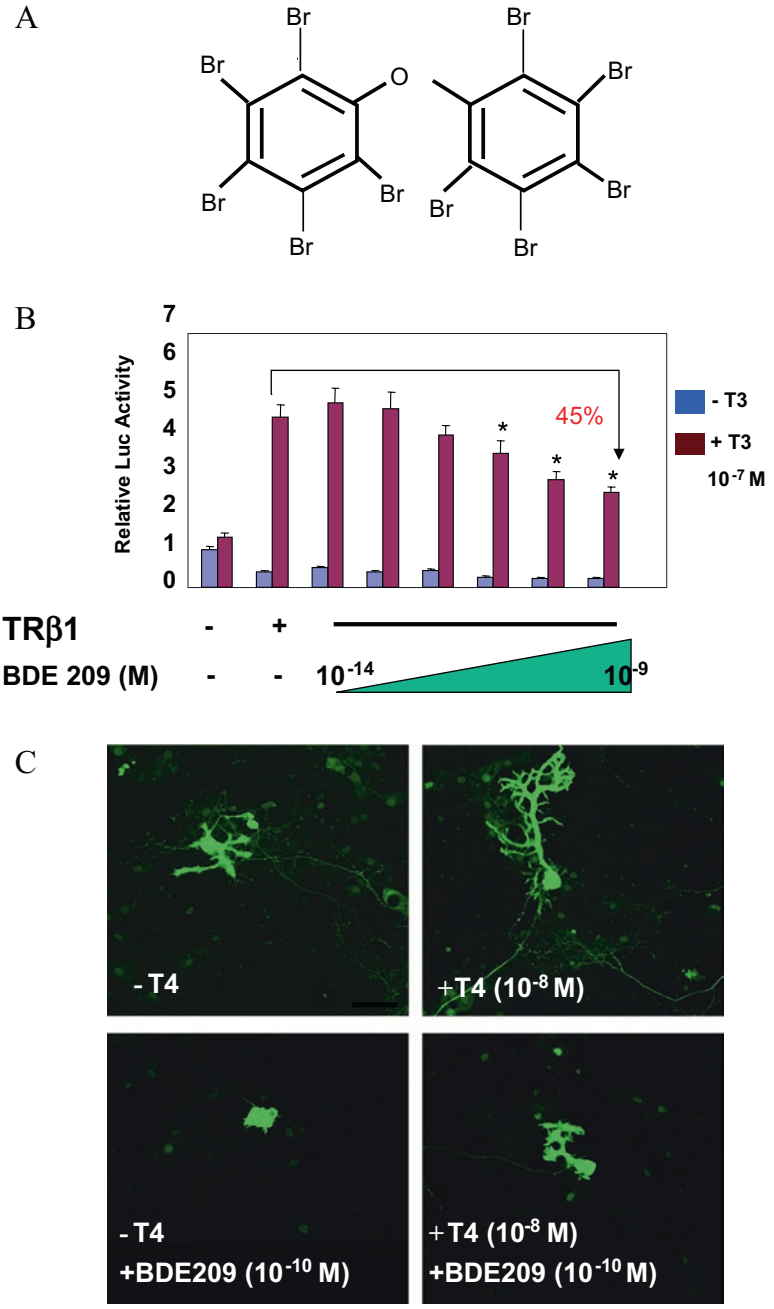

Fig. 7 Representative effect of EDCs (PBDE) on TH-mediated transcription and cerebellar development. (**a**) Chemical structure of BDE209. (**b**) BDE209 suppressed TRβ-mediated transcription, studied by reporter gene assay. *, $p > 0.05$ vs BDE (−) group. (**c**). Effect PBDE (BDE209) on TH-induced Purkinje cell development in primary culture [82]

main reason why such chemicals are not currently defined as EDCs may be that research on EDCs cannot keep up with the increase in newly generated chemicals. Further studies are indeed necessary to identify EDC activity that may cause adverse effect and for the creation of new EDC screening method.

It should be noted that, because concentrations in hormones in plasma are low (nM~pM level), exposure to EDCs, even at low doses, may disrupt hormone action. Furthermore, we do not have the systems to effectively catalyze and excrete most EDCs, because humans are being exposed to EDCs quite recently during the evolutionary process. Thus, EDCs may concentrate in our food chain and accumulate in our body.

So far, 12 chemicals have been identified as being developmental neurotoxic to humans [81]. These are metals and inorganic compounds (arsenic, arsenic compounds, lead, methylmercury, fluoride, and manganese), organic solvents (toluene, tetrachloroethylene), pesticides (chlorpyrifos and DDT/DDE), and industrial chemicals (PCBs and brominated diphenyl ethers [PBDEs]). In cellular or animal study levels, more chemicals may have potential neurotoxic effects [81]. Such chemicals may, at least in part, mediate their action though the endocrine system. In fact, in our previous studies, we have shown that PCBs and PBDEs may disrupt cerebellar development through TH system alterations [15, 82]. Both PCBs and PBDEs inhibit TR-mediated transcription and disrupt TH-induced Purkinje cell development (Fig. 7). Our current study has shown the possibility that several EDCs may affect cerebellar development [15]. Thus, continuous attention should be paid to detect the effect of EDC on cerebellar development. These agents may disrupt cerebellar development even at a low-dose exposure.

Conclusion

Although many hormone receptors are expressed in developing cerebellum, only a limited amount of data is available in this regard. This may a result of the challenges related to research of hormone actions that are mainly mediated by nuclear receptors. Unlike membrane-associated receptors, these act as transcriptional factors to activate or repress the transcription of target genes. Thus, the response is rather slow and various signal transduction cascade may be involved to express their action as a specific phenotype. However, hormonal signaling plays an important role to mediate environmental influences on the developing brain. Thus, hormonal disruptions may cause cerebellar disorders leading to various psychosomatic diseases. It is my hope that this chapter will help increase the understanding of the role of hormones in the developing cerebellum.

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