

We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

5,500

Open access books available

135,000

International authors and editors

165M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?
Contact book.department@intechopen.com

Numbers displayed above are based on latest data collected.
For more information visit www.intechopen.com



Biological Understanding of Neurodevelopmental Disorders Based on Epigenetics, a New Genetic Concept in Education

Takeo Kubota

Abstract

Neurodevelopmental disorders, such as autism spectrum disorder, attention deficit hyperactive disorder, and learning disabilities, are heterogeneous conditions that are thought to have a multifactorial etiology including congenital genetic abnormalities and acquired environmental factors. Epigenetics is a biological mechanism that controls gene expression based on chemical modifications of DNA and chromosomal histone proteins. Environmental factors, such as severe mental stress, have been demonstrated to alter gene expression by changing epigenetic chemical modifications in the brain. Therefore, epigenetics is not only involved in congenital autism spectrum disorder-like conditions (e.g., Prader-Willi syndrome and Rett syndrome) but may also be involved in acquired attention deficit hyperactive disorder-like conditions (e.g., via child abuse and neglect). In this chapter, we introduce the basis of the epigenetic mechanism and the recent biological understanding of neurodevelopmental disorders based on epigenetics, which is a new genetic concept not only in medicine but also in education, which bridges internal brain mechanisms and external environmental factors.

Keywords: epigenetics, environmental factor, neurodevelopmental disorder, ASD, ADHD, child abuse, neglect, reversibility, education

1. Introduction

The number of children with autism spectrum disorder (ASD) is reportedly increasing by 10,000 cases per year in Japan [1], with similar increases observed in other countries, including the USA [2–4] and Korea [5]. These increases can be attributed, in part, to social factors, such as diagnostic substitution whereby children formerly diagnosed with mental retardation are now diagnosed as ASD. However, they cannot be explained fully by such diagnostic substitutions [6], and it is possible that biological changes in the brains of children may also play a role.

Thanks to advances in genomic DNA research, a number of genes associated with ASD have been identified. Mutations in genes encoding synaptic molecules, which facilitate communication between neuronal cells, have been identified in a subset of children with ASD [7, 8]. However, the increase in ASD is unlikely to be simply a result of genetic factors because there is no reason to suspect that mutation

rates have suddenly increased in recent years. Rather, a more likely explanation is that environmental factors are involved.

Epigenetic mechanisms are one of the ways by which gene expression is controlled in higher vertebrates. These mechanisms are essential for normal development during embryogenesis [9] and for the differentiation of various types of cells including neural cells [10, 11]. Therefore, it is important to gain an understanding of epigenetic mechanisms, which include chemical modifications of genetic components such as DNA, histone proteins, and microRNAs. Furthermore, the failure of epigenetic mechanisms results in neurodevelopmental disorders [12–15]. Actually, a number of congenital neurological and mental disorders are reportedly caused by epigenetic abnormalities [16–22].

Epigenetic modifications offer one mechanism by which environmental factors might lead to changes in population health [12]. This is partly supported by studies in twins showing that environmental factors contribute to the occurrence of autism [23–25]. These findings led us to propose the hypothesis that “various environmental factors can change the epigenetic status and alter the expression of a number of neuronal genes (namely synaptic genes), resulting in abnormal brain function (aberrant synaptic function) associated with some neurodevelopmental disorders.”

In this chapter, on the basis of such scientific evidence, we review the current understanding of congenital neurodevelopmental disorders caused by epigenetic abnormalities and also provide a basic description of acquired neurodevelopmental disorders caused by environment-induced epigenetic alterations. Finally, we discuss the future directions of medical and educational interventions for neurodevelopmental disorders (namely ASD).

2. Epigenetic abnormalities in “congenital” neurodevelopmental disorders

Epigenetic gene control is an essential mechanism for normal brain development. Abnormalities in the molecules associated with this process cause various congenital diseases. It is notable that defects in epigenetic phenomena and epigenetic molecules involved in gene regulation result in congenital neurological features and mental retardation. Here, we show four examples.

2.1 Genomic imprinting

Genes are believed to be expressed equally between the maternal and paternal chromosomes. However, an exceptional phenomenon, i.e., genomic imprinting, has been discovered that is the result of an epigenetic gene regulation mechanism. For an imprinted gene, one of the two parental alleles is active and the other is epigenetically inactivated (**Figure 1A**). Therefore, a defect in the active allele of the imprinted gene results in the loss of expression. This has been found in some neurodevelopmental diseases, including Angelman syndrome, which is characterized by severe mental retardation and epilepsy, and Prader-Willi syndrome, which is characterized by neurocognitive deficits, excessive daytime sleepiness, muscle hypotonia, short stature, small hands and feet, hypergonadism, hyperphagia and obesity that leads to type 2 diabetes [26].

2.2 X chromosome inactivation

The X chromosome has a large number of genes, whereas the Y chromosome has relatively few. Thus, females (XX) have more genes than males (XY). To minimize

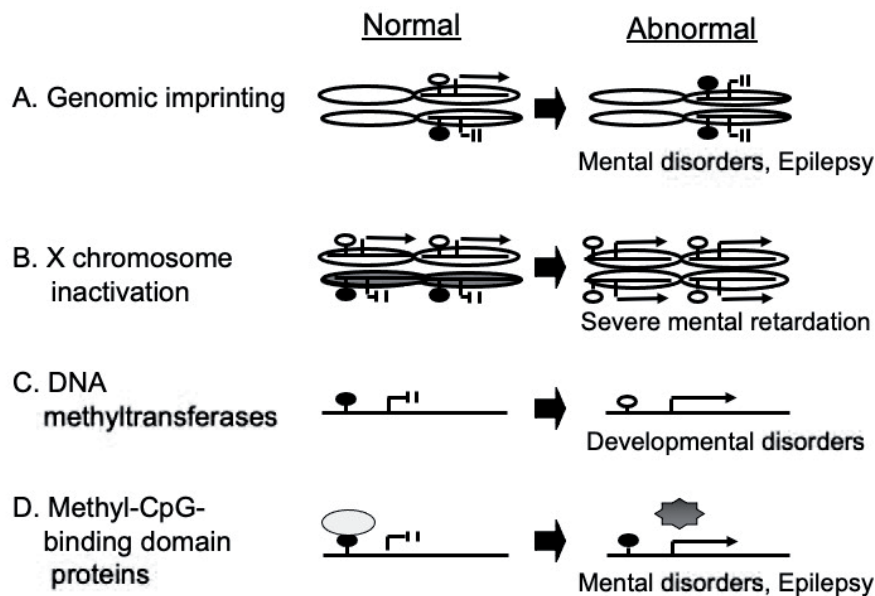


Figure 1.

Mental disorders caused by epigenetic abnormalities. A: Abnormal suppression of the active allele of imprinted genes causes genomic imprinted disorders. B: Abnormal activation of the inactive X chromosome in females causes X-chromosome inactivation disorders. C: Mutations of the genes encode DNA methyltransferase deficiency causes insufficient DNA methylation, which leads aberrant expression of the target genes. D: Mutations of the genes encode methyl-CpG binding proteins causes abnormal regulation of the target genes.

this sex imbalance, one of the two X chromosomes in females is inactivated by an epigenetic mechanism [27]. Improper X chromosome inactivation is thought to be an embryonic lethal condition [28, 29].

When X chromosome inactivation does not occur in women with one normal X chromosome and a small X chromosome due to a large terminal deletion, an over-dosage effect of X-linked genes derived from the small X chromosome leads to severe neurodevelopmental delay [30]. This indicates that proper epigenetic gene regulation is essential for normal development (**Figure 1B**).

2.3 DNA methyltransferases

DNA methylation is a fundamental step in epigenetic gene regulation that is regulated by DNA methyltransferases, which are enzymes that add a methyl group (CH₃) to CpG dinucleotides within human genomic DNA. A defect in a DNA methyltransferase causes ICF syndrome, which is characterized by immunodeficiency, centromere instability, facial anomalies, and mild mental retardation (**Figure 1C**) [18–20].

2.4 Methyl-CpG-binding domain proteins

Methyl-CpG-binding domain proteins are also important molecules in the epigenetic control of gene expression. Abnormalities in the methyl-CpG-binding protein 2 (*MECP2*) gene cause Rett syndrome, which is characterized by seizures, ataxic gait, language dysfunction, and ASD-like behavior [21, 22]. Therefore, abnormal *MECP2* expression in the brain is considered to result in the neurological features of Rett syndrome. In fact, several studies have shown that *MECP2* controls a subset of neuronal genes [29–33], suggesting that epigenetic dysregulation of neuronal genes may cause the neurological features of this disease (**Figure 1D**).

3. Epigenetic abnormalities in “acquired” neurodevelopmental disorders

In neurodevelopmental disorders such as ASD, both environmental factors (e.g., environmental chemicals and infections) and genetic factors (e.g., defects in synaptic molecules) have historically been discussed [4, 8]. However, the biological links between these two groups of factors have not been identified. Epigenetics may bridge these factors in normal and disease development [12].

3.1 Epigenetic bridge between genetic molecules and environmental factors

Besides *intrinsic* (congenital) epigenetic defects (described in Section 2), several lines of evidence suggest that *extrinsic* (environmental) factors, such as malnutrition [34, 35], drugs [36–40], mental stress during the neonatal period [41], and neuronal stimulation [42], alter the epigenetic status, thereby affecting brain function. Therefore, it is intriguing to think that acquired neurodevelopmental disorders, including child abuse- and neglect-induced ADHD-like phenotypes, may be the result of epigenetic dysregulation caused by environmental factors (Figure 2).

3.2 Environmental factors that affect brain function via epigenetic mechanisms

Short-term mental stress after birth may alter gene expression in the brain and result in persistent abnormal behavior (Figure 2).

In rat pups from mothers exhibiting low levels of maternal care, an epigenetic DNA modification in the promoter of the glucocorticoid receptor gene was increased in the hippocampus, leading to the suppressed expression of this gene within the first week of life (Figure 3 right). Conversely, this promoter DNA modification was decreased in the brains of offspring who received high maternal care during the same period (Figure 3 left) [41].

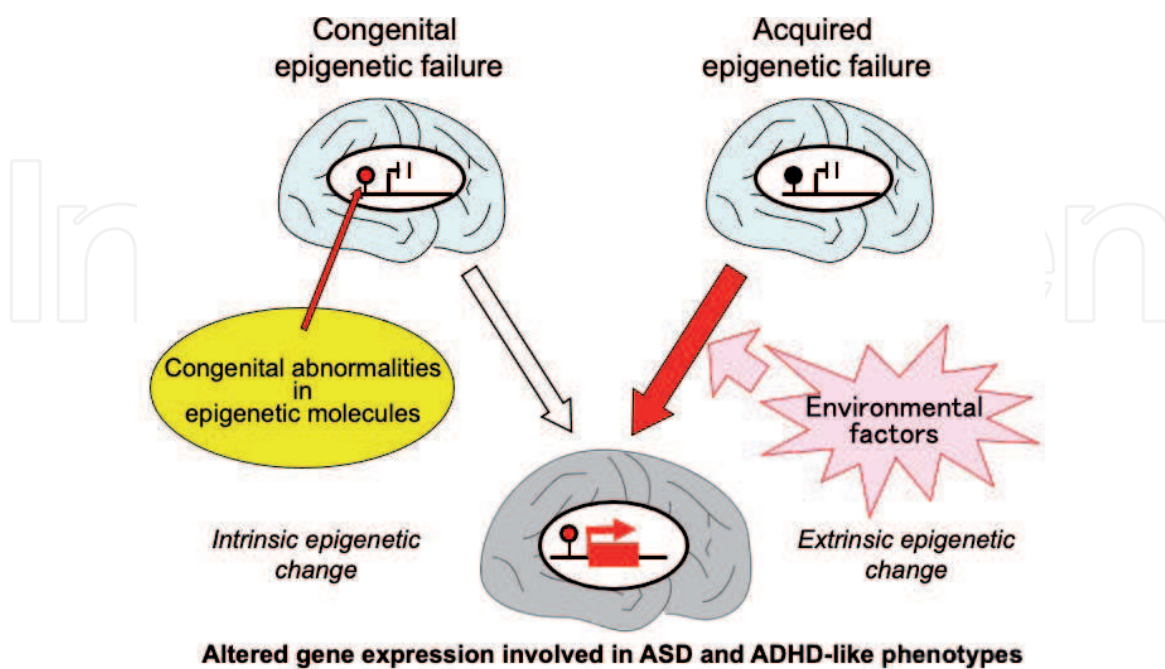


Figure 2.

Current understanding of intrinsic and extrinsic mechanism for neurodevelopmental and mental disorders. Congenital epigenetic disorders are caused by intrinsic mechanism through mutations in the proteins associated with epigenetic gene regulation or epimutation (e.g., de novo DNA methylation) during spermatogenesis and oogenesis. Acquired epigenetic disorders are caused by extrinsic mechanism via various environmental factors.

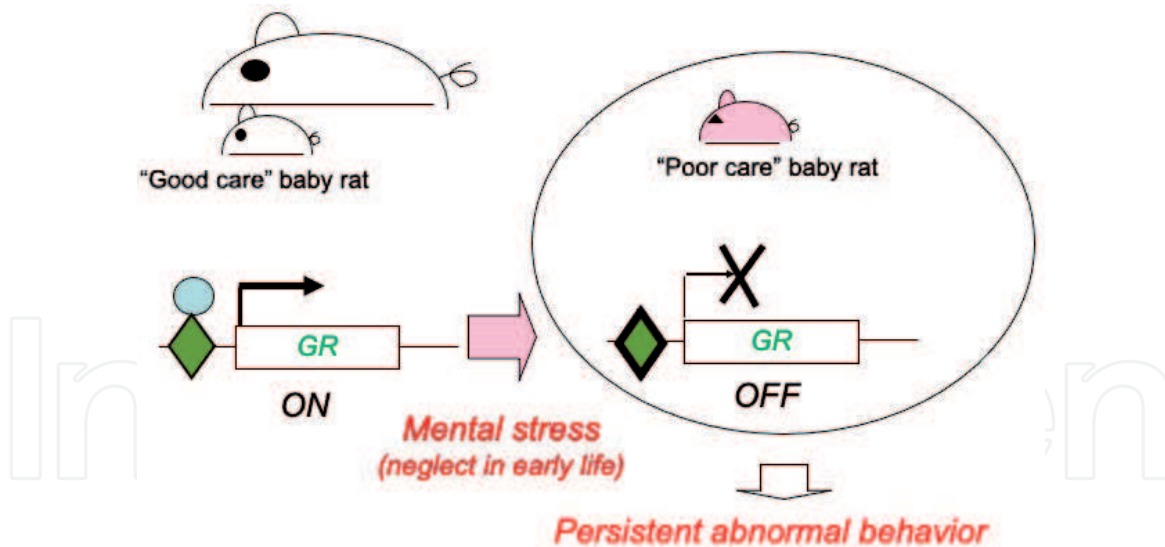


Figure 3. Mental stress-induced DNA methylation changes. Maternal separation-stress during the first week of life induced hypermethylation in the glucocorticoid receptor gene promoter in the mouse hippocampus, and this environment-induced epigenetic changes persists life-time long with abnormal behavior.

This rat experiment provided a putative animal model for childhood neglect and maltreatment in humans. In fact, in a human study, postmortem analysis of the hippocampus of suicide victims with a history of childhood abuse revealed the hyper-modification of the neuron-specific promoter of the glucocorticoid receptor gene in combination with its decreased expression [43]. These findings suggest that the adverse effects of early-life stress on the DNA methylation program may last throughout life [44], and also indicate that neurodevelopmental problems may arise from epigenetic dysregulation caused by environmental factors in early life (**Figure 3**).

A similar epigenetic mechanism is also likely to be relevant in drug addiction. Gene expression in the dopaminergic and glutamatergic systems is mediated by epigenetic mechanisms, and cocaine and alcohol can alter the epigenetic state, which may be associated with permanent behavioral consequences [45, 46].

3.3 Environment-induced epigenetic changes

The above findings were mainly obtained from animal studies, and there is little evidence from humans. However, the fact that epigenomic differences are larger in older monozygotic twins than in younger twins suggests that epigenetic status may be altered during aging by environmental factors in humans [47].

Likewise, the epigenomic patterns of monozygotic twins with discordant severity of Rett syndrome differ and they show differences in the expression of neuronal genes [25]. This indicates that environmental factors may alter the human epigenome and the resulting epigenomic differences may create phenotypic differences between twins.

Birth weight has decreased over the past 20 years, which is thought to be a result of the popularity of dieting among young women and of the recommendation by obstetricians to minimize pregnancy weight gain to reduce the risk of medical problems during pregnancy [48]. According to epidemiological studies of populations affected by famines in the Netherlands and China, offspring with low birth weight are expected to have an increased risk of not only metabolic disorders (e.g., obesity and diabetes mellitus) but also mental disorders [49–51]. Recent studies have demonstrated that malnutrition during the fetal period causes a hypomodification

of the peroxisome proliferator-activated receptor alpha (*PPARα*) gene in the rat liver [52]. Similar epigenetic changes have been identified in people who suffered malnutrition during a period of famine in the Netherlands [53]. The use of assisted reproductive technologies by women, which are now used widely due to increases in the age at which individuals wish to conceive, reportedly decreases the epigenetic modification of DNA at multiple maternally imprinted regions [54, 55].

4. Medical interventions for epigenetics-associated neurodevelopmental disorders

The administration of folic acid to pregnant rats alters the DNA modification status of their offspring [56]. Furthermore, folic acid supplementation to pregnant rats under malnutrition conditions prevents the hypomodification of a hepatic gene in their offspring [57]. In addition to folic acid, various nutritional and other environmental factors, such as royal jelly [58], drugs for mental disorders [36, 38, 40], environmental chemicals [59, 60], and external stimuli (electro-convulsive treatment for psychiatric diseases) [42], have also been demonstrated to alter the DNA or histone modification status of the brain.

As mentioned above, mental stress in the first week of life causes epigenetic abnormalities in the brains of mice. Conversely, several mouse studies have demonstrated that appropriate educational conditions may ameliorate the features of neurodevelopmental disorders. Environmental enrichment, consisting of larger-sized home cages with a variety of objects including running wheels, improves motor coordination and decreases anxiety-related behavior in female mice with an *Mecp2* defect, a model of human Rett syndrome [61, 62]. Environmental enrichment also improves locomotor activity with reduced ventricular volume, and restores the expression of synaptic proteins in the hypothalamus and syntaxin 1a and synaptotagmin expression in the cortex of the brain of these mice [63, 64].

Children with congenital neurodevelopmental disorders caused by genetic defects are considered to be difficult to cure, because it is technically challenging to distribute gene products to the appropriate brain regions and at the appropriate time of development. However, it was recently demonstrated that Rett syndrome may be an exception, partly because *MECP2* is not essential for brain structure, but rather encodes a “lubricant” that works at a relatively later period of brain development. As a consequence, the reintroduction of *MECP2* into mice with a defect in *Mecp2* after birth is sufficient to rescue Rett-like neurological symptoms [65, 66]. Furthermore, the restoration of *MECP2* function in astrocytes substantially improves locomotion, anxiety levels, and respiratory abnormalities in mice with a defect in *Mecp2* [67]. These results suggest that the up-regulation of *MECP2*, possibly mediated by drug treatment, might help to improve the brain function of patients with Rett syndrome. Additionally, these results indicate that neurodevelopmental disorders caused by epigenetic abnormalities can be treated.

5. Educational interventions for epigenetic neurodevelopmental disorders

5.1 Evidence for epigenetic reversibility

Unlike DNA mutations, epigenetic modifications of DNA are reversible, since they are based on the attachment and detachment of chemical residues without any

change to the DNA sequence. Therefore, environmental stress-induced epigenetic abnormalities are potentially reversible, and thus possibly treatable. Here, we show examples.

A mouse study demonstrated that chronic social defeat stress-induced epigenetic alterations can be reversed and brain-derived neurotrophic factor gene expression in the brain can be activated with a commonly used antidepressant (imipramine) by inducing histone acetylation via the down-regulation of histone deacetylases, which ameliorates depression-like behavior [36].

As mentioned above, malnutrition during the fetal period induces the chemical modification of *PPAR α* in the peripheral blood of individuals who suffered malnutrition during a famine in the Netherlands [53] and in the liver of rats fed a protein-restricted diet [52]. However, the protein-restricted diet-induced hypomethylation of *PPAR α* in the offspring could be avoided by supplementation of the diet of maternal rats with folic acid (an essential substrate for methyl residues) [57].

Besides malnutrition, maternal smoking is known to have a negative impact on fetuses, e.g., stillbirth, low birth weight, and small for gestational age, and on offspring, e.g., sudden infant death syndrome, reduced lung function, bronchial asthma, and increased incidence of neurocognitive disorders, tobacco addiction, and obesity [68–70].

Recent cohort studies using cord blood samples originating from fetuses demonstrated that maternal smoking changes DNA methylation at several genes, including a CpG locus in the myosin IG (*MYO1G*) gene. Since *MYO1G* encodes a membrane protein of immune system-associated blood cells [71–74], epigenetic changes in DNA modification presumably down-regulate gene expression, which may be associated with a predisposition to bronchial asthma [73].

Whereas the epigenetic status of *MYO1G* is altered in individuals who smoke during pregnancy, this alteration is not found in individuals who stop smoking during pregnancy, suggesting that smoking-induced alterations in methylation can be reversed by smoking cessation or that they may be produced in a dose-dependent manner during pregnancy [72]. These findings further indicate that smoking cessation during pregnancy may be effective at preventing offspring from developing bronchial asthma (Figure 4). These findings also suggest that the epigenetic mechanism is reversible.

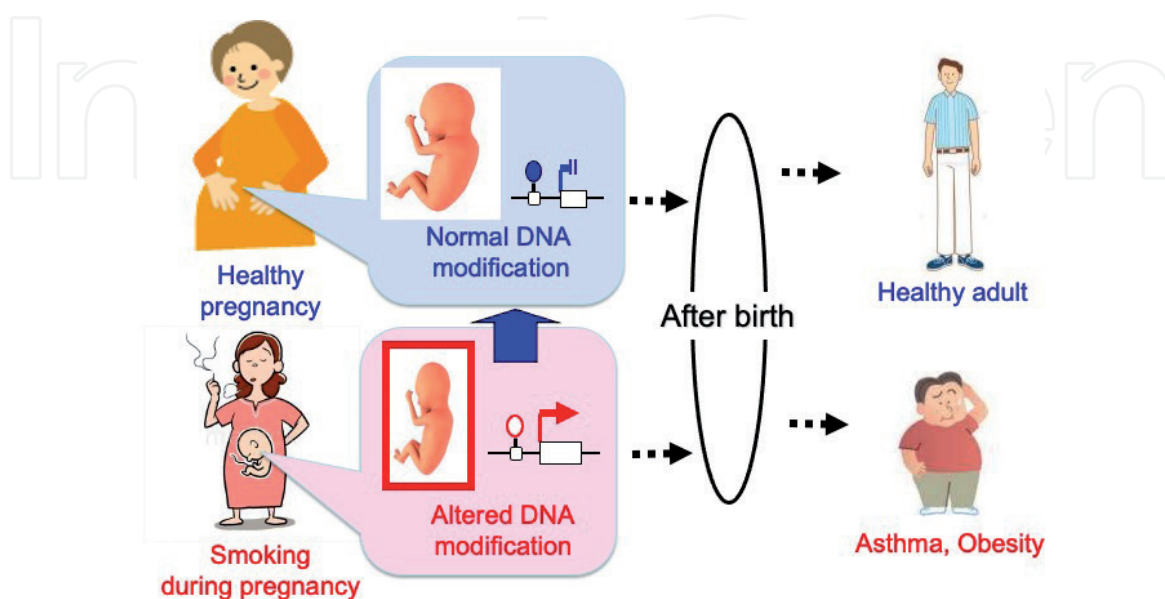


Figure 4. Epigenetic effect of maternal smoking to the fetus. Maternal smoking changes epigenetic state in the fetus, which potentially cause various clinical features, such as bronchial asthma and obesity, in offspring.

5.2 Epigenetic-based early educational intervention

In this chapter, we describe environmental stress-induced epigenetic alterations and their associated disorders. We also discuss the reversibility of the epigenetic mechanism to recover gene expression and potentially ameliorate disease conditions. As a number of molecules associated with epigenetic gene regulation have been identified, pharmacological companies are developing drugs to target these molecules with an aim to correct aberrant gene expression, especially for neurodevelopmental and psychiatric disorders [75].

Besides medical approach, “educational intervention” is another way taking advantage of use of epigenetic reversibility especially for children, because enriched nurturing environment that urged exercise and stimulated brain function ameliorated neurological features, which is demonstrated in a mouse model of Rett syndrome that is an autistic disorder caused by failure of epigenetic gene regulation as mentioned above [62–64]. Therefore, understanding of the epigenetic reversible concept is important for all staffs in a preschool and a nursery school, because they are the caregivers who will be able to urge development of children who had an adverse experience before and after birth, by offering appropriate nurture and education.

6. Conclusion

It was reported that the number of children with ASD is increasing in various countries including US and Japan. When we think of biological mechanism for this increase, one can imagine that some factors in recent society increased ASD via epigenetic mechanism based on chemical modification of DNA and histone proteins which control gene expression in the children’s brain.

It has been known that abnormalities in epigenetic mechanisms lead to congenital neurodevelopmental disorders, such as Rett syndrome characterized by seizures, ataxic gait, language dysfunction, and ASD-like behavior.

Besides congenital epigenetic abnormalities, several lines of evidence suggest that environmental factors also alter the epigenetic status of brain-function associated genes. Therefore, it is intriguing to think that child abuse and neglect-induced ADHD-like phenotypes, which are thought to be increased in modern society, may be the result of epigenetic dysregulation caused by mental stress in early life.

Recent medical research demonstrated that some nutrients and drugs for mental illness reversed the epigenetic state and recover healthy physical and mental condition, and revealed that epigenetics is a reversible and thus treatable mechanism.

Besides such medical approach, “educational intervention” is another way taking advantage of use of epigenetic reversibility especially for children, because enriched nurturing environment that urged exercise and stimulated brain function ameliorated neurological features in mouse experiments. Therefore, epigenetics, described in this chapter, will be essential concept that contribute to future nurture and education.

In conclusion, epigenetics becomes a new genetic concept not only in medicine but also in education, which bridges internal brain mechanisms and external environmental factors.

Acknowledgements

The research described in this chapter was partially supported by the Ministry of Education, Science, Sports and Culture (MEXT), Grants-in-Aid (KAKENHI)

for Exploratory Research (#18 K18663; to TK), and for Scientific Research (C) (#21 K028887; to TK).

Conflict of interest

The authors declare no conflict of interest.

IntechOpen

IntechOpen

Author details

Takeo Kubota
Professional Degree Course, Graduate School of Teacher Education, Seitoku
University, Matsudo, Japan

*Address all correspondence to: kubota.takeo@wa.seitoku.ac.jp

IntechOpen

© 2021 The Author(s). Licensee IntechOpen. This chapter is distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/3.0>), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited. 

References

- [1] Basic investigation report for handicapped children 2005 (in Japanese). Available from: <http://www.mhlw.go.jp/toukei/saikin/hw/titeki/index.html> [Accessed: 2021-7-13]
- [2] Yeargin-Allsopp M, Rice C, Karapurkar T, Doernberg N, Boyle C, Murphy C. Prevalence of autism in a US metropolitan area. *JAMA*. 2003;289:49-55.
- [3] Holoden, C. Autism Now. *Science* 2009;323:565.
- [4] Fombonne E. Epidemiology of pervasive developmental disorders. *Pediatr Res* 2009;65:591-598.
- [5] Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry* 2011;168:904-912.
- [6] Lord C. Epidemiology: How common is autism? *Nature* 2011;474:166-168.
- [7] Zoghbi HY. Postnatal neurodevelopmental disorders: meeting at the synapse? *Science* 2003;302:826-830.
- [8] Persico AM, Bourgeron T. Searching for ways out of the autism maze: genetic, epigenetic and environmental clues. *Trends Neurosci* 2006; 29:349-358.
- [9] Li E, Beard C, Jaenisch R. Role for DNA methylation in genomic imprinting. *Nature* 1993;366:362-365.
- [10] Takizawa T, Nakashima K, Namihira M, Ochiai W, Uemura A, Yanagisawa M, et al. DNA methylation is a critical cell-intrinsic determinant of astrocyte differentiation in the fetal brain. *Dev Cell* 2001;1:749-758.
- [11] Sakashita K, Koike K, Kinoshita T, Shiohara M, Kamijo T, Taniguchi S, et al. Dynamic DNA methylation change in the CpG island region of p15 during human myeloid development. *J Clin Invest* 2001;108:1195-1204.
- [12] Qiu J. Epigenetics: unfinished symphony. *Nature* 2006;441:143-145.
- [13] Abel T and Zukin RS. Epigenetic targets of HDAC inhibition in neurodegenerative and psychiatric disorders. *Curr Opin Pharmacol* 2008;8:57-64.
- [14] Urdinguio RG, Sanchez-Mut JV, Esteller M, et al. Epigenetic mechanisms in neurological diseases: genes syndromes and therapies. *Lancet Neurol* 2009;8:1056-1072.
- [15] Wu H, Tao J, Chen PJ, Shahab A, Ge W, Hart RP, et al. Genome-wide analysis reveals methyl-CpG-binding protein 2-dependent regulation of microRNAs in a mouse model of Rett syndrome. *Proc Natl Acad Sci U S A* 2010;107:18161-18166.
- [16] Kubota T, Das S, Christian SL, Baylin SB, Herman JG, Ledbetter DH. Methylation-specific PCR simplifies imprinting analysis. *Nat Genet* 1997;16:16-17.
- [17] Kubota T, Wakui K, Nakamura T, Ohashi H, Watanabe Y, Yoshino M, et al. Proportion of the cells with functional X disomy is associated with the severity of mental retardation in mosaic ring X Turner syndrome females. *Cytogenet Genome Res* 2002;99:276-284.
- [18] Okano M, Bell DW, Haber DA, Li E: DNA methyltransferases Dnmt3a and Dnmt3b are essential for de novo methylation and mammalian development. *Cell* 1999;99:247-257.
- [19] Shirohzu H, Kubota T, Kumazawa A, Sado T, Chijiwa T,

- Inagaki K, et al. Three novel DNMT3B mutations in Japanese patients with ICF syndrome. *Am J Med Genet* 2002; 112:31-37.
- [20] Kubota T, Furuumi H, Kamoda T, Iwasaki N, Tobita N, Fujiwara N, et al. ICF syndrome in a girl with DNA hypomethylation but without detectable DNMT3B mutation. *Am J Med Genet A* 2004;129:290-293.
- [21] Amir RE, Van den Veyver IB, Wan M, Tran CQ, Francke U, Zoghbi HY. Rett syndrome is caused by mutations in X-linked MECP2 encoding methyl-CpG-binding protein 2. *Nat Genet* 1999;23:185-188.
- [22] Chunshu Y, Endoh K, Soutome M, Kawamura R, Kubota T. A patient with classic Rett syndrome with a novel mutation in MECP2 exon 1. *Clin Genet* 2006;70:530-531.
- [23] Hoekstra RA, Bartels M, Hudziak JJ, Van Beijsterveldt TC, Boomsma DI. Genetics and environmental covariation between autistic traits and behavioral problems. *Twin Res Hum Genet* 2007; 10: 853-886.
- [24] Hallmayer, J., Cleveland, S., Torres, A., Phillips, J., Cohen, B., Torigoe T, et al. Genetic heritability and shared environmental factors among twin pairs with autism. *Arch Gen Psychiatry* 2011;68:1095-1102.
- [25] Miyake K, Yang C, Minakuchi Y, Ohori K, Soutome M, Hirasawa T, Kazuki Y, et al. Comparison of genomic and epigenomic expression in monozygotic twins discordant for Rett syndrome. *PLoS ONE* 8:e66729, 2013.
- [26] Kubota T, Nonoyama S, Tonoki H, Masuno M, Imaizumi K, Kojima M, et al. A new assay for the analysis of X-chromosome inactivation based on methylation-specific PCR. *Hum Genet* 1999;104:49-55.
- [27] Xue F, Tian XC, Du F, Kubota C, Taneja M, Dinnyes A, et al. Aberrant patterns of X chromosome inactivation in bovine clones. *Nat Genet* 2002;31: 216-220.
- [28] Nolen LD, Gao S, Han Z, Mann MR, Gie CY, Otte AP, et al. X chromosome reactivation and regulation in cloned embryos. *Dev Biol* 2005;279:525-540.
- [29] Chen WG, Chang Q, Lin Y, Meissner A, West AE, Griffith EC, et al. Derepression of BDNF transcription involves calcium-dependent phosphorylation of MeCP2. *Science* 2003;302:885-889.
- [30] Martinowich K, Hattori D, Wu H, Fouse S, He F, Hu Y, et al. DNA methylation-related chromatin remodeling in activity-dependent BDNF gene regulation. *Science* 2003;302: 890-893.
- [31] Horike S, Cai S, Miyano M, Cheng JF, Kohwi-Shigematsu T. Loss of silent-chromatin looping and impaired imprinting of DLX5 in Rett syndrome. *Nat Genet* 2005;37:31-40.
- [32] Itoh M, Ide S, Takashima S, Kudo S, Nomura Y, Segawa M, et al. Methyl CpG-binding protein 2 (a mutation of which causes Rett syndrome) directly regulates insulin-like growth factor binding protein 3 in mouse and human brains. *J Neuropathol Exp Neurol* 2007;66:117-123.
- [33] Miyake K, Hirasawa T, Soutome M, Itoh M, Goto Y, Endoh K, et al. The protocadherins, PCDHB1 and PCDH7, are regulated by MeCP2 in neuronal cells and brain tissues: implication for pathogenesis of Rett syndrome. *BMC Neurosci.* 2011;12:81.
- [34] Burdige GC, Lillycrop KA, Phillips ES, Slater-Jefferies JL, Jackson AA, Hanson MA. Folic Acid Supplementation during the Juvenile-Pubertal Period in Rats Modifies the

Phenotype and Epigenotype Induced by Prenatal Nutrition. *J Nutr* 2009;139:1054-1060.

[35] Lillycrop KA, Slater-Jefferies JL, Hanson MA, Godfrey KM, Jackson AA, Burdge GC. Induction of altered epigenetic regulation of the hepatic glucocorticoid receptor in the offspring of rats fed a protein-restricted diet during pregnancy suggests that reduced DNA methyltransferase-1 expression is involved in impaired DNA methylation and changes in histone modifications. *Br J Nutr* 2007;97:1064-1073.

[36] Tsankova NM, Berton O, Renthal W, Kumar A, Neve RL, Nestler EJ. Sustained hippocampal chromatin regulation in a mouse model of depression and antidepressant action. *Nat Neurosci* 2006;9:519-525.

[37] Jessberger S, Nakashima K, Clemenson GD Jr, Mejia E, Mathews E, Ure K, et al. Epigenetic Modulation of Seizure-Induced Neurogenesis and Cognitive Decline. *J Neurosci* 2007;27:5967-5975.

[38] Dong E, Nelson M, Grayson DR, Costa E, Guidotti A. Clozapine and sulpiride but not haloperidol or olanzapine activate brain DNA demethylation. *Proc Natl Acad Sci USA* 2008;105:13614-13619.

[39] Dong E, Chen Y, Gavin DP, Grayson DR, Guidotti A. Valproate induces DNA demethylation in nuclear extracts from adult mouse brain. *Epigenetics* 2010;5:730-735.

[40] Wang Q, Xu X, Li J, Liu J, Gu H, Zhang R, et al. Lithium, an anti-psychotic drug, greatly enhances the generation of induced pluripotent stem cells. *Cell Res* 2011;21:1424-1435.

[41] Weaver IC, Cervoni N, Champagne FA, D'Alessio AC, Sharma S, Seckl JR, et al. Epigenetic

programming by maternal behavior. *Nat Neurosci* 2004;9:847-854.

[42] Ma DK, Jang MH, Guo JU, Kitabatake, Y, Chang ML, Pow-Anpongkul N, et al. Neuronal Activity-Induced Gadd45b Promotes Epigenetic DNA Demethylation and Adult Neurogenesis. *Science* 2009;323:1074-1077.

[43] McGowan PO, Sasaki A, D'Alessio AC, Dymov S, Labonté B, Szyf M, et al. Epigenetic regulation of the glucocorticoid receptor in human brain associates with childhood abuse. *Nat Neurosci* 2009;12:342-348.

[44] Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, Fischer D, et al. Dynamic DNA methylation programs persistent adverse effects of early-life stress. *Nat Neurosci* 2009;12:1559-1566.

[45] Renthal W, Kumar A, Xiao G, Wilkinson M, Covington HE 3rd, Maze I, et al. (2009). Genome-wide analysis of chromatin regulation by cocaine reveals a role for sirtuins. *Neuron* 62, 335-348.

[46] Pascual M, Boix J, Felipe V, Guerri C. Repeated alcohol administration during adolescence causes changes in the mesolimbic dopaminergic and glutamatergic systems and promotes alcohol intake in the adult rat. *J Neurochem* 2009;108:920-931.

[47] Fraga MF, Ballestar E, Paz MF, Ropero S, Setien F, Ballestar ML, et al. Epigenetic differences arise during the lifetime of monozygotic twins. *Proc Natl Acad Sci USA* 2005;102:10604-10609.

[48] Gluckman PD, Seng CY, Fukuoka H, Beedle AS, Hanson MA. Low birthweight and subsequent obesity in Japan. *Lancet* 2007;369:1081-1082.

[49] Painter RC, de Rooij SR, Bossuyt PM, Simmers TA, Osmond C,

- Barker DJ, et al. Early onset of coronary artery disease after prenatal exposure to the Dutch famine. *Am J Clin Nutr* 2006;84:322-327.
- [50] St Clair D, Xu M, Wang P, Yu Y, Fang Y, Zhang F, Zheng X, et al. Rates of adult schizophrenia following prenatal exposure to the Chinese famine of 1959-1961. *JAMA* 2005;294:557-562.
- [51] Silveira PP, Portella AK, Goldani MZ, Barbieri MA. Developmental origins of health and disease (DOHaD). *J Pediatr (Rio J)* 2007;83:494-504.
- [52] Lillycrop KA, Phillips ES, Torrens C, Hanson MA, Jackson AA, Burdge GC: Feeding pregnant rats a protein-restricted diet persistently alters the methylation of specific cytosines in the hepatic PPAR alpha promoter of the offspring. *Br J Nutr* 2008;100:278-282.
- [53] Tobi EW, Lumey LH, Talens RP, Kremer D, Putter H, Stein AD, et al. DNA methylation differences after exposure to prenatal famine are common and timing- and sex-specific. *Hum Mol Genet* 2009;18:4046-4053.
- [54] Lim D, Bowdin SC, Tee L. Clinical and molecular genetic features of Beckwith-Wiedemann syndrome associated with assisted reproductive technologies. *Hum Reprod* 2009; 24:741-747.
- [55] Bliiek J, Alders M, Maas SM, Oostra RJ, Mackay DM, van der Lip K, et al. Lessons from BWS twins: complex maternal and paternal hypomethylation and a common source of haematopoietic stem cells. *Eur J Hum Genet* 2009;17:1625-16534.
- [56] Waterland RA, Jirtle RL. Transposable elements: targets for early nutritional effects on epigenetic gene regulation. *Mol Cell Biol* 2003;23:5293-5300.
- [57] Lillycrop KA, Phillips ES, Jackson AA, Hanson MA, Burdge GC. Dietary protein restriction of pregnant rats induces and folic acid supplementation prevents epigenetic modification of hepatic gene expression in the offspring. *J Nutr* 2005;135: 1382-1386.
- [58] Kucharski R, Maleszka J, Foret S, Maleszka R. Nutritional control of reproductive status in honeybees via DNA methylation. *Science* 2008;319:1827-1830.
- [59] Yaoi T, Itoh K, Nakamura K, Ogi H, Fujiwara Y, Fushiki S. Genome-wide analysis of epigenomic alterations in fetal mouse forebrain after exposure to low doses of bisphenol A. *Biochem Biophys Res Commun* 2008;376:563-567.
- [60] Gore AC, Walker DM, Zama AM, Armenti AE, Uzumcu M. Early life exposure to endocrine-disrupting chemicals causes lifelong molecular reprogramming of the hypothalamus and premature reproductive aging. *Mol Endocrinol* 2011;25:2157-2168.
- [61] Kondo M, Gray LJ, Pelka GJ, Christodoulou J, Tam PP, Hannan AJ. Environmental enrichment ameliorates a motor coordination deficit in a mouse model of Rett syndrome-Mecp2 gene dosage effects and BDNF expression. *Eur J Neurosci* 2008;27:3342-3350.
- [62] Lonetti G, Angelucci A, Morando L, Boggio EM, Giustetto M, Pizzorusso T. Early environmental enrichment moderates the behavioral and synaptic phenotype of MeCP2 null mice. *Biol Psychiatry* 2010;67:657-665.
- [63] Nag N, Moriuchi JM, Peitzman CG, Ward BC, Kolodny NH, Berger-Sweeney JE. Environmental enrichment alters locomotor behaviour and ventricular volume in Mecp2 1lox mice. *Behav Brain Res* 2009;196:44-48.

- [64] Kerr B, Silva PA, Walz K, Young JI. Unconventional transcriptional response to environmental enrichment in a mouse model of Rett syndrome. *PLoS One* 2010;5:e11534.
- [65] Luikenhuis S, Giacometti E, Beard CF, Jaenisch R. Expression of MeCP2 in postmitotic neurons rescues Rett syndrome in mice. *Proc Natl Acad Sci USA* 2004;101:6033-6038.
- [66] Guy J, Gan J, Selfridge J, Cobb S, Bird A. Reversal of neurological defects in a mouse model of Rett syndrome. *Science* 2007;315:1143-1147.
- [67] Liou DT, Garg SK, Monaghan CE, Raber J, Foust KD, Kaspar BK, et al. A role for glia in the progression of Rett's syndrome. *Nature* 2011;475:497-500.
- [68] Murin S, Rafii R, Billello K. Smoking and smoking cessation in pregnancy. *Clin Chest Med* 2011;32:75-91. DOI: 10.1016/j.ccm.2010.11.004.
- [69] Burke H, Leonardi-Bee J, Hashim A, Pine-Abata H, Chen Y, Cook DG, Britton JR, McKeever TM. Prenatal and passive smoke exposure and incidence of asthma and wheeze: systematic review and meta-analysis. *Pediatrics*. 2012 Apr;129(4):735-44. DOI: 10.1542/peds.2011-2196. Epub 2012 Mar 19.
- [70] Lee JW, Jaffar Z, Pinkerton KE, Porter V, Postma B, Ferrini M, Holian A, Roberts K, Cho YH. Alterations in DNA methylation and airway hyperreactivity in response to in utero exposure to environmental tobacco smoke. *Inhal Toxicol* 2015;27(13):724-730. DOI: 10.3109/08958378.2015.1104402. Epub 2015 Nov 2.
- [71] Richmond RC, Simpkin AJ, Woodward G, Gaunt TR, Lyttleton O, McArdle WL, Ring SM, Smith AD, Timpson NJ, Tilling K, Davey Smith G, Relton CL. Prenatal exposure to maternal smoking and offspring DNA methylation across the lifecourse: findings from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Hum Mol Genet* 2015 Apr 15;24(8):2201-2217. DOI: 10.1093/hmg/ddu739. Epub 2014 Dec 30.
- [72] Miyake K, Kawaguchi A, Miura R, Kobayashi S, Tran NQV, Kobayashi S, Miyashita C, Araki A, Kubota T, Yamagata Z, Kishi R. Association between DNA methylation in cord blood and maternal smoking: The Hokkaido Study on Environment and Children's Health. *Sci Rep* 2018 Apr 4;8(1):5654. DOI: 10.1038/s41598-018-23772-x.
- [73] Richmond RC, Suderman M, Langdon R, Relton CL, Sith GD. DNA methylation as a marker for prenatal smoke exposure in adults. *Int J Epidemiol*. 2018 Aug 1;47(4):1120-1130. DOI: 10.1093/ije/dyy091.
- [74] Online Mendelian Inheritance of Men (OMIM) #600642 Available from: <https://www.ncbi.nlm.nih.gov/omim/600642> [Accessed: 2021-7-13]
- [75] Szyf M. Prospects for the development of epigenetic drugs for CNS conditions. *Nature Review of Drug Discovery* 14, 461-474, (2018). *Nat Rev Drug Discov*. 2015;14(7):461-474. DOI: 10.1038/nrd4580. Epub 2015 May 22.