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ARCHIVES OF MEDICINE
ISSN 1989-5216

2017
Vol.9 No.6:2

DOI: 10.21767/1989-5216.1000244

Antiepileptic Drugs and Developmental Neuroendocrine Dysfunction: Every Why has A Wherefore

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Received date: November 14, 2017; **Accepted date:** November 17, 2017; **Published date:** November 20, 2017

Citation: Ahmed RG (2017) Antiepileptic drugs and developmental neuroendocrine dysfunction: Every why has A Wherefore. Arch Med Vol No:9 Iss No:6:2

Keywords: Antiepileptic drugs; Thyroid gland; GH-releasing hormone

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Normal thyroid functions are required during the perinatal development [1-39]. During the last years, antiepileptic drugs (AEDs) such as sodium valproate (VPA) [40-42], phenobarbital(PB) [40], carbamazepine (CBZ) [43], phenytoin (PHT) [40] and lamotrigine (LTG) [41,44] and gabapentin (GBP, second generation AEDs) can alter the fetal development, and cause a neuronal injury [45], teratogenic effects [46,47] and several congenital malformations [48-50]. Also, they can decrease the levels of thyroid hormones (THs), inhibit the $Na+/I^-$ symporter and the iodide (I^-) utilization [51], eliminate THs and stimulate TH-glucuronoconjugation [52]. AEDs may interact with hypothalamo-pituitary axis, synthesis of GH-releasing hormone (GHRH) and its metabolism via stimulating [53,54] or inhibiting the hormone metabolism [54]. This may be due to disruption of the activities of THs that may delay growth [10,55], and loss of anabolism during the hypothyroidism [56].

On the other hand, AEDs might induce the epileptogenesis [57], mental retardation [58], severe neuronal migration disorders, neuronal cell death, cortical deformation and developing brain distortion [59]. This may be due to CBZ blocked the voltage-dependent sodium channels [60], and decreased the density [61,62] and permeability of these channels during the early developmental period [63]. These disturbances might be attributed to the imbalance in the maternofetal THs-axis (hypothyroidism) as suggested by Ahmed et al. [29]. This might influence, generally, on the health of the fetuses depending on the degree of the maternofetal hypothyroidism and fetal TH-brain dysfunctions.

On the other hand, the skeletal anomalies were found in fetuses of rats after the maternal exposure to GBP or VPA (Singh et al., 2014). However, these anomalies were more significant in VPA than GBP. In humans and animals, the teratogenic effects of GBP such as delayed ossifications and skeletal deformations are inconsistent and inconclusive due to the environmental and molecular mechanisms, GBP doses, route and time of administration, animal species and sex type [64-66]. Importantly, the fetal skeletal system is more sensitive to GBP during organogenesis in different animal models such as rats [67], mice [68,69] and chick [70]. GBP or VPA can cross the placenta and accumulate in several fetal organs delaying the osteogenesis and chondrogenesis [71-77]. These variations might be attributed to GBP or VPA can alter the maternofetal mineral and trace elements [78]. In rats, the maternal exposure to 400 mg VPA significantly reduced the level of zinc (Zn, critical for the organogenesis) in both dams and their embryo's [79]. The deficiency in Zn [67,79] and fluctuation in the concentration of GABA (γ-aminobutyric acid) neurotransmitter [66]might be caused skeletal teratogenicity. Thus, Zn may play an important role in the calcification and bone mineralization during the organogenesis [68,69,80]. However, extrapolation of animal investigations to clinics should be importantly scrutinized.

On the basis of these data, it can be concluded that the administration of AEDs may cause dysfunctions in the communication between dams and their fetuses, and in the developmental thyroid-brain axis. These effects might depend on the concentration and period of administration of AEDs, and sex type and developmental period of animal species. Additional studies are necessary to clarify the potential associations with human health. Future examinations are needed to explore whether the effect of maternal AEDs on the developmental neuroendocrine system (THs-brain axis) and the cytokines markers play a role in modifying the signaling pathways related to the cellular proliferation and cell death during the perinatal period.

Conflict of Interest

The author declares that no competing financial interests exist.

References

1. El-bakry AM, El-Ghareeb AW, Ahmed RG (2010) Comparative study of the effects of experimentally-induced hypothyroidism and hyperthyroidism in some brain regions in albino rats. Int J Dev Neurosci 28: 371-389.

2. Ahmed RG (2017) Maternal dioxin and fetal neuroendocrine dysfunction. MRJMMS. In press.
3. Ahmed OM, Abd El-Tawab SM, Ahmed RG (2010) Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: I- The development of the thyroid hormones-neurotransmitters and adenosinergic system interactions. Int J Dev Neurosci 28: 437-454.
4. Ahmed OM, Ahmed RG (2012) Hypothyroidism. In a new look at hypothyroidism. Dr. D. Springer edn., Tech Open Access Publisher, pp: 1-20.
5. Ahmed OM, Ahmed RG, El-Gareib AW, El-Bakry AM, Abd El-Tawaba SM (2012) Effects of experimentally induced maternal hypothyroidism and hyperthyroidism on the development of rat offspring: II-The developmental pattern of neurons in relation to oxidative stress and antioxidant defense system. Int J Dev Neurosci 30: 517-537.
6. Ahmed OM, El-Gareib AW, El-bakry AM, Abd El-Tawab SM, Ahmed RG (2008) Thyroid hormones states and brain development interactions. Int J Dev Neurosci 26: 147-209.
7. Ahmed RG (2011) Perinatal 2, 3, 7, 8-tetrachlorodibenzo-p-dioxin exposure alters developmental neuroendocrine system. Food Chem Toxicology 49: 1276-1284.
8. Ahmed RG (2012) Maternal-newborn thyroid dysfunction. In the Developmental Neuroendocrinology. LAP LAMBERT Academic Publishing GmbH & Co KG., Germany, pp: 1-369.
9. Ahmed RG (2012) Maternal-fetal thyroid interactions. Thyroid Hormone, Dr. NK Agrawal edn., Tech Open Access Publisher, pp: 125-156.
10. Ahmed RG (2013) Early weaning PCB 95 exposure alters the neonatal endocrine system: Thyroid adipokine dysfunction. J Endocrinol 219: 205-215.
11. Ahmed RG (2014) Do PCBs modify the thyroid-adipokine axis during development? Annals Thyroid Res 1: 11-12.
12. Ahmed RG (2015) Hypothyroidism and brain development. J Anim Res Nutr 2:13.
13. Ahmed RG (2015)Hypothyroidism and brain developmental players. J Thyroid Res 8: 1-12.
14. Ahmed RG (2015) Maternofetal thyroid action and brain development. J adv Biol 7: 1207-1213.
15. Ahmed RG (2015) Developmental adipokines and maternal obesity interactions. J adv Biol 7: 1189-1206.
16. Ahmed RG (2016) Maternal bisphenol A alters fetal endocrine system: Thyroid adipokine dysfunction. Food Chem Toxicol 95: 168-174.
17. Ahmed RG (2016) Gestational dexamethasone alters fetal neuroendocrine axis. Toxicol Lett 258: 46-54.
18. Ahmed RG (2016) Maternal iodine deficiency and brain disorders. Endocrinol Metab Syndr 5: 223.
19. Ahmed RG (2016) Neonatal polychlorinated biphenyls-induced endocrine dysfunction. Ann Thyroid Res 2: 34-35.
20. Ahmed RG (2017) Developmental thyroid diseases and GABAergic dysfunction. EC Neurology 8: 02-04.
21. Ahmed RG (2017) Hyperthyroidism and developmental dysfunction. Arch Med 9: 1-2.
22. Ahmed RG (2017) Anti-thyroid drugs may be at higher risk for perinatal thyroid disease. EC Pharmacol Toxicol 4: 140-142.
23. Ahmed RG (2017) Perinatal hypothyroidism and cytoskeleton dysfunction. Endocrinol Metab Syndr 6: 271.
24. Ahmed RG (2017) Developmental thyroid diseases and monoaminergic dysfunction. Adv Appl Sci Res 8: 01-10.
25. Ahmed RG (2017) Hypothyroidism and brain development. J Anim Res Nutr 2: 13.
26. Ahmed RG, Abdel-Latif M, Ahmed F (2015) Protective effects of GM-CSF in experimental neonatal hypothyroidism. Int J Immunopharmacol 29: 538-543.
27. Ahmed RG, Abdel-Latif M, Mahdi E, El-Nesr K (2015) Immune stimulation improves endocrine and neural fetal outcomes in a model of maternofetal thyrotoxicosis. Int Immunopharmacol 29: 714-721.
28. Ahmed RG, Davis PJ, Davis FB, De Vito P, Farias RN, et al. (2013) Nongenomic actions of thyroid hormones: From basic research to clinical applications. An update. Immunol Endocr Metab Agents Med Chem 13: 46-59.
29. Ahmed RG, El-Gareib AW (2014) Lactating PTU exposure: I- Alters thyroid-neural axis in neonatal cerebellum. EJBMSR 2: 1-16.
30. Ahmed RG, El-Gareib AW (2017) Maternal carbamazepine alters fetal neuroendocrine-cytokines axis. Toxicology 382: 59-66.
31. Ahmed RG, El-Gareib AW, Incerpi S (2014) Lactating PTU exposure: II- Alters thyroid-axis and prooxidant-antioxidant balance in neonatal cerebellum. IRJNS 2: 1-20.
32. Ahmed RG, Incerpi S (2013) Gestational doxorubicin alters fetal thyroid–brain axis. Int J Dev Neurosci 31: 96-104.
33. Ahmed RG, Incerpi S, Ahmed F, Gaber A (2013) The developmental and physiological interactions between free radicals and antioxidant: Effect of environmental pollutants. J Natural Sci Res 3: 74-110.
34. Candelotti E, De Vito P, Ahmed RG, Luly P, Davis PJ, et al. (2015) Thyroid hormones crosstalk with growth factors: Old facts and new hypotheses. Immunol Endocr Metab Agents Med Chem 15: 71-85.
35. De Vito P, Candelotti E, Ahmed RG, Luly P, Davis PJ, et al. (2015) Role of thyroid hormones in insulin resistance and diabetes. Immun Endoc & Metab Agents in Med Chem 15: 86-93.
36. El-Ghareeb AA, El-Bakry AM, Ahmed RG, Gaber A (2016) Effects of zinc supplementation in neonatal hypothyroidism and cerebellar distortion induced by maternal carbimazole. AJAS 4: 1030-1040.
37. Incerpi S, Hsieh MT, Lin HY, Cheng GY, De Vito P, et al. (2014) Thyroid hormone inhibition in L6 myoblasts of IGF-I-mediated glucose uptake and proliferation: New roles for integrin αvβ3. Am J Physiol Cell Physiol 307: C150-C161.
38. Van Herck SLJ, Geysens S, Bald E, Chwatko G, Delezie E, et al. (2013) Maternal transfer of methimazole and effects on thyroid hormone availability in embryonic tissues. Endocrinol 218: 105-115.
39. Gigena N, Alamino VA, Montesinos MM, Nazar M, Louzada RA, et al. (2017) Dissecting thyroid hormone transport and metabolism in dendritic cells. J Endocrinology 232: 337-350.
40. Bittigau P, Sifringer M, Ikonomidou C (2003) Antiepileptic drugs and apoptosis in the developing brain. Ann N Y Acad Sci 993: 103-114.
41. Manent JB, Ben-Ari Y, Represa A (2008) Antiepileptic drugs and pregnancy: Brain malformations in rats prenatally exposed to lamotrigine, vigabatrin and valproate. Epilepsies 20: 27-32.

42. Sabers A, Bertelsen FC, Scheel-Kruger J, Nyengaard JR, Moller A (2014) Long-term valproic acid exposure increases the number of neocortical neurons in the developing rat brain: A possible new animal model of autism. Neurosci Lett 580: 12-16.

43. Aberg E, Holst S, Neagu A, Ogren SO, Lavebratt C (2013) Prenatal exposure to carbamazepine reduces hippocampal and cortical neuronal cell population in new-born and young mice without detectable effects on learning and memory. PloS one 8: e80497.

44. Marchi NS, Azoubel R, Tognola WA (2001) Teratogenic effects of lamotrigine on rat fetal brain: A morphometric study. Arq Neuropsiquiatr 59: 362-364.

45. Ikonomidou C, Turski L (2010) Antiepileptic drugs and brain development. Epilepsy Res 88: 11-22.

46. Faiella A, Wernig M, Consalez GG, Hostick U, Hofmann C, et al. (2000) A mouse model for valproate teratogenicity: Parental effects, homeotic transformations, and altered HOX expression. J Hum Mol Genet 9: 227-236.

47. Pennell PB (2005) Using current evidence in selecting antiepileptic drugs for use during pregnancy. Epilepsy Curr 5: 45-51.

48. Samren EB, Van Duijn CM, Christiaens GCML, Hofman A, Lindhout D (1999) Antiepileptic drug regimens and major congenital abnormalities in the offspring: Annals of Neurol 46: 739-746.

49. Vajda FJ, O'Brien TJ, Lander CM, Graham J, Eadie MJ (2014) The teratogenicity of the newer antiepileptic drugs - An update. Acta Neurol Scand 130: 234-238.

50. Weston JBR, Jackson CF, Adab N, Clayton-Smith J, Greenhalgh J, et al. (2016) Monotherapy treatment of epilepsy in pregnancy: Congenital malformation outcomes in the child. Cochrane Database Syst Rev.

51. Isojärvi JIT, Turkka J, Pakarinen AJ, Kotila M, Rättyä J, et al. (2001) Thyroid function in men taking carbamazepine, oxcarbazepine, or valproate for epilepsy. Epilepsia 42: 930-934.

52. Simko J, Horacek J (2007) Carbamazepine and risk of hypothyroidism: A prospective study. Acta Neurol Scand 116: 317-321.

53. Yüksel A, Yalcin E, Cenani A (1993) Influence of long-term carbamazepine treatment on thyroid function. Acta Paediatr Jpn 35: 229-232.

54. Leskiewicz M, Budziszewska B, Lason W (2008) Endocrine effects of antiepileptic drugs. Przegl Lek 65: 795-798.

55. Ahima RS, Flier JS (2000) Adipose tissue as an endocrine organ. Trends Endocrinol Metab 11: 327-332.

56. Robson H, Siebler T, Shalet SM, Williams GR (2002) Interactions between GH, IGF-I, glucocorticoids and thyroid hormones during skeletal growth. Pediatric Research 52: 137-147.

57. Koch S, Titze K, Zimmermann RB, Schroder M, Lehmkuhl U, et al. (1999) Long-term neuropsychological consequences of maternal epilepsy and anticonvulsant treatment during pregnancy for schoolage children and adolescents. Epilepsia 40: 1237-1243.

58. Barkovich AJ, Raybaud CA (2004) Neuroimaging in disorders of cortical development. Neuroimaging Clin N Am 14: 231-254.

59. Manent JB, Jorquera I, Mazzucchelli I, Depaulis A, Perucca E, et al. (2007) Fetal exposure to GABA-acting antiepileptic drugs generates hippocampal and cortical dysplasias. Epilepsia 48: 684-693.

60. White HS (1999) Comparative anticonvulsant and mechanistic profile of the established and newer antiepileptic drugs. Epilepsia 40: S2-S10.

61. Sitges M, Sanchez-Tafolla BM, Chiu LM, Aldana BI, Guarneros A (2011) Vinpocetine inhibits glutamate release induced by the convulsive agent 4-aminopyridine more potently than several antiepileptic drugs. Epilepsy Res 96: 257-266.

62. Gómez CD, Buijs RM, Sitges M (2014) The anti-seizure drugs vinpocetine and carbamazepine, but not valproic acid, reduce inflammatory IL-1β and TNF-α expression in rat hippocampus. J Neurochem 130: 770-779.

63. Manent JB, Demarque M, Jorquera I, Pellegrino C, Ben Ari Y, et al. (2005) A noncanonical release of GABA and glutamate modulates neuronal migration. J of Neurosci 25: 4755-4765.

64. Montouris G (2003) Gabapentin exposure in human pregnancy: Results from the gabapentin pregnancy registry. Epilepsy Behav 4: 310–317.

65. Prakash, Prabhu LV, Rai R, Pai MM, Yadav SK, et al. (2008). Teratogenic effects of the anticonvulsant gabapentin in mice. Singapore Med J 49: 49–53.

66. Afshar M, Mohammad M, Taheri H, Moallem SA, Tamizi A, et al. (2009) Teratogenic effects of gabapentin on the skeletal system of Balb/C mice fetuses. Neurosciences 14: 239–244.

67. Akbari M, Abolhassani F, Azizi M, Dehpour AR, Ansari M, et al. (2004) Altered plasma zinc level contributes to the developmental toxicity of valproic acid in skeletal system of rat. Acta Medica Iranica 42: 10–15.

68. Padmanabhan R, Ahmed I (1996) Sodium valproate augments spontaneous neural tube defects and axial skeletal malformations into mouse fetuses. Reprod Toxicol 10: 345–363.

69. Okada A, Kurihara H, Aoki Y, Bialer M, Fujiwara M (2004) Amidic modification of valproic acid reduces skeletal teratogenicity in mice. Birth Defects Res (B) Dev. Birth Defects Res B 71: 47–53.

70. Whitsel AI, Johnson CB, Forehand CJ, (2002) An in vivo chicken model to study the systemic and localized teratogenic effects of valproic acid. Teratology 66: 153–163.

71. Carter DR, Orr TE, Fyhrie DP, Schurman DJ (1987) Influences of mechanical stress on prenatal and postnatal skeletal development. Clin Orthop Relat Res 219: 237–250.

72. Rodriguez, JI, Palacios J, Garcia-Alix A, Pastor I, Paniagua R (1988) Effects of immobilization on fetal bone development. A morphometric study in newborns with congenital neuromuscular diseases with intrauterine onset. Calcif Tissue Int 43: 335–339.

73. Frost HM, Jee WS (1994) Perspectives: A vital biomechanical model of the endochondral ossification mechanism. Anat Rec 240: 435–446.

74. Rauch F, Schoenau E (2001) The developing bone: Slave or master of its cells and molecules? Pediatr Res 50: 309–314.

75. Zuscik MJ, Hilton MJ, Zhang X, Chen D, O'Keefe RJ (2008) Regulation of chondrogenesis and chondrocyte differentiation by stress. J Clin Invest 118: 429–438.

76. Shim M, Foley J, Anna C, Mishina Y, Eling T (2010) Embryonic expression of cyclooxygenase-2 causes malformations in axial skeleton. J Biol Chem 285: 16206–16217.

77. Fadel RA, Sequeira RP, Abu-hijleh MF, Obeidat M, Salem AHA (2012) Effect of prenatal administration of therapeutic doses of topiramate on ossification of ribs and vertebrae in rat fetuses. Rom J Morphol Embryol 53: 321–327.

78. Vormann J, Hillriegl V, Merker HJ, Günther T (1986) Effect of valproate on zinc metabolism in fetal and maternal rats fed normal and zinc deficient diets. Biol Trace Element Res 10: 25–35.

79. Keen CL, Peters JM, Hurley LS (1989) The effect of valproic acid on 65 Zn distribution in the pregnant rat. J Nutr 119: 607–611.

80. Salgueiro MJ, Zubillaga MB, Lysionek AE, Sarabia MI, Caro RA (2000) Bioavailability, biodistribution and toxicity of bio Zn–AAS: A new zinc source comparative studies in rats. Nutrition 16: 762–766.