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

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Rapid Communication

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+/Iˉ symporter and the iodide (Iˉ) utilization [51], eliminate THs and stimulate TH-glucuronon conjugation [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.

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