

THE EFFECTS OF HYPO- AND HYPERVITAMINOSIS A AND ITS INVOLVEMENT IN FOETAL NERVOUS SYSTEM DEVELOPMENT AND POST-NATAL SENSORIMOTOR FUNCTIONING - A REVIEW

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Introduction

The purpose of this paper is to investigate the effects of hypo- and hypervitaminosis A on foetal nervous system development and post-natal sensorimotor functioning, and we propose that altered programmed foetal nervous system development may give rise to post-natal learning disabilities involving all forms of sensorimotor learning, vestibular functioning, eye and visual system deficits, disrupted sleep rhythms as well as altered mood and emotional processes. Sufficient intake of micronutrients during pregnancy is essential; however, the kinds of problems and pitfalls that may arise from uninformed dietary planning

are multi-faceted. The following scenario perhaps typifies the kind of problems that the pregnant mother may encounter:

Following a so-called healthy diet, the pregnant mother starts off her day with 40 to 60 gram of cereal, representing 20 to 30% of the recommended daily allowance of vitamin A, in addition to vitamin supplements that are taken in tablet form, adding an additional 100% vitamin A to her daily intake. Further snacks and meals consist of dairy products, vitamin-enriched cereal foods, fruits, vegetables, eggs, fish, oils and butter or margarine. Very often different brands of over-the-counter vitamins and minerals are taken, without considering the possibility of exceeding the maximum daily allowance,

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and which may impact on programmed foetal nervous system development. In addition, there seems to be an increase among children suffering from mild neurological impairments such as attention deficits, poor balance, enduring fatigue, reading and writing difficulties, poor sense of timing and synchronisation, as well as compromised sensorimotor integration; yet this tendency cannot satisfactorily be explained.

In the light of the possible adverse effects of hypervitaminosis A, the research question directing this article is formulated as follows: What are the effects of hypo- and hypervitaminosis A and its involvement in foetal nervous system development and post-natal sensorimotor functioning?

Analysis of Research Questions

Vitamin A is one of the fat-soluble vitamins that are necessary for the normal functioning of the human body, and it was first identified to be essential for the developing embryo in 1933 by Hale (Hale, 1933). The requirement of vitamin A for normal embryonic and foetal development is known from many nutritional studies (Wolf, 1984; Blomhoff, 1994; Zile, 2004). Almost all steps in organogenesis are controlled by retinoic acids, thus suggesting that retinol is necessary for normal development of embryonic tissues (Perrotta *et al.*, 2003). Vitamin A has an essential role in the development of organs such as the lungs (Zachman, 1995; Massaro *et al.*, 2000; Mendelson, 2000; Cardoso, 2001; Biesalski and Nohr, 2003), heart (Ross *et al.*, 2000) and skeleton (Yamaguchi *et al.*, 1998). Retinoic acid also enables the setting up of vascular and nervous systems (Ross *et al.*, 2000; Maden, 2001a; Colbert, 2002).

The supply of vitamin A or related

compounds called retinoids to the foetus is essential, as they are involved in growth and cellular differentiation (Zachman, 1995; Debier and Larondelle, 2005). The term retinoids include both the naturally occurring forms of vitamin A and the many synthetic analogues of retinol, with or without a biological activity (Blomhoff, 1994; Debier and Larondelle, 2005). Vitamin A is transferred to the embryo from the maternal circulation, and the transfer of retinol, retinaldehyde, and retinoic acid has been well documented following the administration of large doses of these compounds to pregnant animals (Collins *et al.*, 1994; Kraft *et al.*, 1987; Kochhar *et al.*, 1988; Kraft *et al.*, 1989; Ward and Morriss-Kay, 1995; Sass *et al.*, 1999; Clagett-Dame and DeLuca, 2002). This transplacental transfer is tightly regulated by the homeostasis of the mother. However, with prolonged exposure of pathological levels of vitamin A, the maternal homeostasis is disrupted, this disruption may lead to teratogenicity.

During the period of early foetal development the supply of vitamin A must be carefully managed to ensure that the developing foetus is exposed to neither too little nor too much vitamin A, because either condition can have teratogenic consequences. Towards the end of gestation, adequate maternal vitamin A status and dietary intakes are important to maximise the vitamin A transferred to the foetus in preparation for parturition and lactation.

Although this important vitamin is very necessary in the normal development of the foetus, a high intake while the mother is pregnant, may be detrimental to the early development of the foetus (Cohlan, 1953; McCaffery *et al.*, 2003) and it may also have a detrimental impact on the learning and development of the young child. However, except for abnormal

foetal development caused by an excess of vitamin A intake, a vitamin A deficiency or a deficiency of retinoids may cause abnormal morphological development (teratogenesis) in several organs or systems in the foetus/embryo. The defects produced are remarkably similar in deficiency and excess, suggesting modulation of common developmental or cellular processes by different levels of retinoids. The different forms of vitamin A found in animal tissues are retinol (vitamin A₁ alcohol), retinal (vitamin A₁ aldehyde), retinoic acid and retinyl esters (Blomhoff 1994; Debier and Larondelle 2005). In 1967, Kochhar showed that retinoic acid was of much greater potency than vitamin A (Kochhar, 1967), but it took a further 20 years before it was determined that retinoic acid was more teratogenic because this was the transcriptional active retinoid that bound specific nuclear receptors (Giguère *et al.*, 1987; Petkovich *et al.*, 1987; McCaffery *et al.*, 2003). However, the importance and location of the foetal malformation depends on the period of gestation and the duration of the excessive or deficient supply (Bates, 1983; Ross *et al.*, 2000; Stoilov, 2001; Pasqualetti and Rijli, 2001; Debier and Larondelle, 2005).

Literature Review

Hypo- and hypervitaminosis A involvement in foetal nervous system development

Studies from as early as the 1920's found that in the absence of retinoic acid adult animal become sterile, the mucous epithelium transforms into keratinised epithelium and the immune function is severely compromised (Wolbach and Howe, 1925; Underwood, 1984; Ross and

Hammerling, 1994; Maden, 2000), therefore retinoic acid is involved in immunity and reproduction as well as in the regulation of pattern formation in the early embryo (Eskild and Hansson, 1994; Maden, 1994; Ross and Gardner, 1994; Napoli, 1999; Debier and Larondelle, 2005). Retinol seems to have an important role to play in reproduction while retinal is essential for vision (Thompson *et al.*, 1963; Olson, 1984; Chew, 1993; Blomhoff, 1994; Eskild and Hansson, 1994; Debier and Larondelle, 2005).

Potential vitamin A sources come from dietary intake, nutritional supplements, and some therapeutic drugs. Vitamin A in the diet originates either in the form of retinyl esters from animal tissues or as pro-vitamin A (mainly β -carotene) from plant tissues. The main sources of vitamin A in food are dairy products, liver, eggs and fish oils. The carotene or carotenoids refer to vitamin A precursors (pro-vitamin A) and can be found in fruits and green or yellow vegetables as well as in several types of oils. β -Carotene is one of the most abundant carotenoids (During and Harrison, 2004; Debier and Larondelle, 2005). The Vitamin A that is obtained from the diet is stored in the liver in form of retinyl esters (Blomhoff, 1994; Maden, 2000). To release this stored form, the esters are hydrolysed to retinol, which are released into the bloodstream for transport round the body bound to plasma retinol-binding protein. Cells which require retinoic acid take up retinol and convert it to retinoic acid through the action of two types of enzymes.

Vitamin A is required for reproduction. Evans in 1928 showed that the depletion of vitamin A prior to the mating of the rats, either prevented implantation or produced foetal resorption (Evans, 1928). Morriss-Kay and Sokolova (1996) reported on vitamin A deficient mice that also showed a very poor reproductive outcome. Therefore, it is

clear that an adequate amount of vitamin A is necessary for reproduction, even though sometimes a few foetuses survive with malformations.

A variety of experimental approaches (Rosa *et al.*, 1986; Teratology Society, 1987; Hendrickx *et al.*, 1997; Dolk *et al.*, 1999) have been used to study the importance of vitamin A signalling in developing embryos, including the embryonic exposure to insufficient and excessive retinoid at various stages of development by maternal dietary manipulation and use of retinoid antagonists, as well as genetic approaches. Importantly, it is now known that different organs, including the brain of the developing foetus may be compromised due to vitamin A excess as well as deficiency. TABLE I shows the

different organ systems affected by vitamin A deficiency and excess.

In this review we will discuss how vitamin A deficiency as well as an excess intake of this important vitamin may affect foetal development which will ultimately impact on early development of the child.

Vitamin A deficiency and how it impacts on foetal nervous system development

The earliest evidence that the deficiency of vitamin A could produce congenital malformations was described in 1933 (Hale, 1933). Most research conducted on how the abnormalities presented, used animal models. Animal models are used in order to correlate time of exposure and

TABLE I
Areas of foetal anatomy that are compromised due to vitamin A excess as well as deficiency

Organ systems affected	Excess of vitamin A	Deficiency of vitamin A
Craniofacial structures	Eye anomalies Cleft palate External ear defects Mandibular hypoplasia	Eye defects Midline facial clefts Underdeveloped palatal shelves Hypoplastic mandible
Lungs		Squamos metaplasia of the tracheal and bronchial epithelium
Heart	Heart malformations	Lack of heart looping and chamber morphogenesis Enlarged anterior cardinal veins Abnormality in the developing sinuatrial venous valve
Skeleton (limbs)	Limb defects	Shortening of the trunk region Absence of limb buds Forelimb abnormalities Loss of digits Persistent webbing of the digits Reduction in limb length Supernumerary postaxial element
Central nervous system	Neural tube defects Hydrocephalus Microencephaly	Incomplete neural tube closure Abnormalities in the developing hindbrain Hydrocephalus
Diaphragm		Herniated
Kidneys	Failure of kidney development	Horseshoe shaped Reduction in nephron number

doses to abnormalities observed due to accidental human exposure. Defects seen in animals can be correlated to those in humans. However, animal studies give researchers a controlled environment to study teratogenicity. Abnormalities due to vitamin A deficiency include craniofacial defects or defects to eyes (Clagett-Dame and DeLuca, 2002), kidney defects and diaphragm (herniated) abnormalities. Eye abnormalities include offspring that were born without eyes, only one eye present, one large and one small eye, offspring that were born blind, retarded retinal development, absence of the vitreous body or retinal eversion (Hale, 1933; White, 1999). Other defects occurring at a lower frequency included cleft palate, hare lip, accessory external ears, and the arrested ascension of the kidneys. It was this research that initially established that a nutritional as opposed to a hereditary factor, was responsible for the observed defects.

The term “vitamin A-deficiency syndrome” was created in the 1940’s and further described in the 1950’s, after a series of experiments appeared describing the production of a large array of congenital defects in the rat that could be attributed to vitamin A deficiency (Jackson and Kinsey, 1946; Warkany and Schraffenberger, 1946; Wilson and Barch, 1949; Wilson and Warkany, 1948; Wilson and Warkany, 1949; Warkany, 1945; Warkany *et al.*, 1948).

Morriss-Kay and Sokolova (1996) reported in a review on surviving mouse fetuses with midline facial clefts, underdeveloped palatal shelves, hypoplastic mandible, and forelimb abnormalities (loss of digits, persistent webbing of the digits, reduction in limb length, and a supernumerary postaxial element).

White and co-workers (1998) reported that due to deficiency of vitamin A, rat

embryos were grossly abnormal, including incomplete spiral torsion of the tail, reduction of forelimb size, and defects in eye development. Importantly, abnormalities in the region of the developing hindbrain were noted. The majority of embryos exhibited cardiovascular abnormalities, including enlarged anterior cardinal veins and an abnormality in the developing sinuatrial venous valve (White *et al.*, 2000a). Most of the embryos died when maternal diets were more severely vitamin A restricted. The few embryos that did survive, failed to survive beyond the 16-somite stage and showed no evidence of hindbrain segmentation (White *et al.*, 2000b). It is also noteworthy that the posterior hindbrain and heart tube were adversely affected in the vitamin A deficient (VAD) quail (Maden, 2001b; Zile, 2001; Heine *et al.*, 1985). Thus, patterning of the early central nervous system, as well as the development of the cardiac inflow tract in both the bird and the mammal, appears dependent upon adequate vitamin A (Clagett-Dame and DeLuca 2002). White and co-workers (White *et al.*, 2000a) suggested that embryonic death occurring at midgestation in the VAD rat may be linked to the abnormal development of the primitive heart tube and the posterior hindbrain. It seems that the hindbrain is the most susceptible part of the central nervous system (CNS) to altered levels of retinoic acid (Maden, 2001a).

Niederreither and co-workers (Niederreither *et al.*, 2000) perturbed the key enzymes involved in the biosynthetic pathway leading to the generation of all-trans retinoic acid (a form of vitamin A). The homozygous null mutant mice displayed severe embryonic abnormalities, including impaired body turning (axial rotation), a lack of heart looping and chamber morphogenesis, incomplete neural tube closure, shortening of the

trunk region, and absence of limb buds. The hindbrain region of these embryos was also severely disrupted, and morphological segmentation was impaired.

Vitamin A deficient new born dairy calves were examined and some of the gross lesions included hydrocephalus and thickened occipital and sphenoid bones. Some other abnormalities included constriction of the optic nerves as a result of a reduction in size and dorsoventral narrowing of the optic canals. Microscopically changes in the optic nerves were characterised by necrosis (a form of cell death), demyelination (loss of the myelin sheath of a nerve or nerves) and fibrosis (formation of scar-like tissue). Oedema (swelling due to the retention of fluids in the tissues) or gliosis (proliferation of glial cells in the damaged CNS portion) of the optic disc occurred in some of the calves. Retinal lesions included atrophy and gliosis of the ganglion cell layer and the nerve fibre layer (van der Lugt and Prozesky, 1989).

Retinoids even play an extremely important role in blood formation. Oren and co-workers (Oren *et al.*, 2003) reported on the importance of retinoid requirements in hematopoiesis.

Specific defects in organ systems due to vitamin A deficiency were noted by various researches. These will now briefly be discussed.

Congenital hydrocephalus is associated with deficiency of vitamin A (Fiuza Perez 1953; Millen *et al.*, 1953; Millen *et al.*, 1954; Lamming *et al.*, 1954). In addition Chytil suggested that vitamin A is involved in lung development (Chytil, 1985). They established the following:

Dietary deficiency of the fat-soluble vitamin A results in squamous metaplasia of the tracheal and bronchial epithelium.

Infants with vitamin A deficiency have a high incidence of respiratory problems.

Levels of two intracellular binding proteins, specifically retinol (vitamin A alcohol) and retinoic acid (vitamin A acid), change dramatically during perinatal lung development. Prematurely born infants hospitalised for respiratory problems have low serum concentrations of retinol and retinol-binding protein. Postnatal supply of vitamin A by parenteral alimentation may not be adequate, as large quantities of vitamin A are absorbed by the tubing.

Congenital diaphragmatic hernia is associated with high neonatal mortality and morbidity due to pulmonary hypoplasia and pulmonary hypertension. Antioxidant vitamins A, E, and C given late in gestation alleviate heart hypoplasia that accompanies congenital diaphragmatic hernia (Gonzalez-Reyes *et al.*, 2005). Greer *et al.* (2003) outline evidence suggesting that abnormalities linked with the retinoid signalling pathway early in gestation may contribute to the etiology of congenital diaphragmatic hernia.

Vitamin A supply to the foetus is critical in determining the number of nephrons in the kidney (Lelievre-Pegorier *et al.*, 1998). Even mild foetal vitamin A-deficiency syndrome can result in a reduction of nephron number (Burrow, 2000). Retinoids have an essential function in branching growth of the ureteric bud (Burrow, 2000).

Epidemiological and laboratory evidence support a hypothesis that there may be genetic (recessive) predisposition to the teratogenic effects of mild to moderate maternal VAD during pregnancy. This may explain the higher prevalence of congenital eye anomalies in a part of Asian countries, where maternal VAD is common and consanguineous marriages are popular (Hornby *et al.*, 2003).

Vitamin A excess and how it impacts on foetal nervous system development

Vitamin A and its derivatives, retinoic acid, tretinoin and isotretinoin, are currently used in dermatological treatments. Isotretinoin has been shown to have teratogenic effects causing primarily heart and craniofacial malformations, including ear and palatal defects (de la Cruz *et al.*, 1984; Hansen and Pearl, 1985; Goulding and Pratt, 1986). In 1983 the American Academy of Dermatology requested its members to relate the outcome of pregnancies of women inadvertently exposed to isotretinoin (Accutane)(13-cis-retinoic acid) during pregnancy to its Adverse Drug Reaction Reporting system (ADRRS). Spontaneous abortion resulted in 83% of the pregnancies reported (Stern *et al.*, 1984). The birth defects that were reported involved the central nervous system (microcephaly or hydrocephaly) (Lott *et al.*, 1984) and the cardiovascular system (anomalies of the great vessels). Microtia or absence of external ears were also noted in the majority of cases (Lott *et al.*, 1984; Stern *et al.*, 1984; Lammer *et al.*, 1985).

Studies with exogenously applied retinoids have been used to manipulate and perturb normal embryonic development and have provided evidence that almost every organ or tissue system can be severely affected. Foetal resorptions, abortions and stillbirths are linked to excessive consumption of vitamin A and its derivatives. Examination of aborted and stillborn foetuses disclosed hydrocephalus, microencephaly, and cleft palate (Pilotti, 1955; DiGiacomo *et al.*, 1992).

Morphologically palate clefting in retinoic acid treatment results in the foetus presenting with either extreme hypoplasia (underdevelopment) or agenesis (imperfect development) of the palatal shelves and

associated with astomia (absence of a mouth), microstomia (unusually small mouth), aglossia (absence of the tongue), microglossia (unusually small tongue) and micrognathia (unnaturally small jaw) with fusion of mandible, maxilla, and zygoma (Padmanabhan and Ahmed, 1997).

Administering excessive vitamin A during the pre-implantation period as well as during pregnancy cause eye anomalies which included open eyelids, exophthalmia (protrusion of the eyeballs), cataractous lens, microphthalmia (unnatural smallness of the eyes) and anophthalmia (congenital absence of all eye tissues) (Padmanabhan *et al.*, 1981; Pillans *et al.*, 1988; Emmanouil-Nikoloussi *et al.*, 2000).

A wide spectrum of craniofacial defects, including exencephaly (defective skull with the brain exposed or extruding) (Pillans *et al.*, 1988), maxillo-mandibular dysostosis, mandibular hypoplasia, micrognathia of both maxilla and mandible, cleft palate, subdevelopment of ear lobe, external ear defects, preauricular tags, temporal bone abnormalities and macroglossia (abnormally large tongue), are seen in the offspring of overexposed animals to retinoids (Hendrickx and Hummler, 1992; Emmanouil-Nikoloussi *et al.*, 2000).

Retinoic acid is an effective inducer of cleft palate (Hendrickx and Hummler, 1992; Degitz *et al.*, 1998; Mohanty and Singh, 2000; Emmanouil-Nikoloussi *et al.*, 2000). Exogenous all-trans retinoic acid has pleiotropic effects on the pattern of odontogenesis when applied before the formation of the dental lamina. These effects include a change in the pattern of the dental lamina, supernumerary buds and incisors in the diastema region, and replacement of molars with incisors in the molar region (Kronmiller *et al.*, 1995). Balducci-Roslondo *et al.*, (2001) compared the tooth germs of the first maxillary and mandibular molars of fetal mice submitted

to isotretinoin during organogenesis. The first molar germs of the isotretinoin-treated animals showed delayed development compared to the control animals.

High concentrations of retinoids occur in some commercial cat food formulations as a result of the use of animal liver as an ingredient. The teratogenic potential of dietary vitamin A in kittens was investigated by Freytag *et al.*, in 2003. Some of the malformations included cleft palate, cranioschisis, foreshortened mandible, stenotic colon, enlarged heart and agenesis of the spinal cord and small intestine, which are typical foetal defects consistent with ingestion of excess retinoids in other species.

Retinoic acid is necessary for normal differentiation of the tail bud into the secondary tube. Excess retinoic acid, however, is teratogenic and causes neural tube defects (NTDs) (Griffith and Zile, 2000). As early as 1978, Stange and co-workers reported on a case of malformations of the foetal central nervous system following hypervitaminosis A in early pregnancy (Stange *et al.*, 1978). Induced delivery resulted in a microcephalic child who died after 18 minutes. The child had multiple malformations of the central nervous system and very small adrenal glands.

Hindbrain herniation and caudal lumbosacral myelorachischisis, in addition to a variety of other craniofacial and caudal malformations, occur after exposure to all-trans-retinoic acid (Alles and Sulik, 1992).

Vitamin A metabolites, especially retinoic acid, are known to play an important role in limb development (Underhill and Weston, 1998; Zhou and Kochhar, 2004). Severe limb defects are produced if it is administered at a certain stage of embryonic development (Kochhar, 1985; Pillans *et al.*, 1988). Some species have the capacity to regenerate amputated limbs, and retinoids certainly affect this

process, but there is debate regarding the extent that regeneration recapitulates development (Lee *et al.*, 2004).

Specific cardiovascular targets of retinoid action include effects on the anteroposterior patterning of the early heart, left-right decisions and cardiac situs, endocardial cushion formation, and in particular, the neural crest (Colbert, 2002).

Exposure of pregnant animals to all-trans retinoic acid, at a time when the metanephros has yet to form, causes a failure of kidney development along with caudal regression (Tse *et al.*, 2005).

Vitamin A involvement in post-natal sensorimotor functioning

The preceding literature study suggests that hypo- and hypervitaminosis A during gestation might affect the foetus adversely. Almost all steps in organogenesis are controlled by retinoic acids (Perrotta *et al.*, 2003), with specific focus on foetal nervous system development and hindbrain development (Ross *et al.*, 2000; Maden 2001a; Colbert 2002). In addition, the supply of retinoids to the foetus is essential, as these are involved in neural growth and cellular differentiation (Zachman, 1995; Debier and Larondelle, 2005), which might impact on post-natal sensorimotor learning. The cerebellum is of particular interest, due to involvement in almost all forms of motor learning and vestibular functioning. The cerebellum consists of the cerebellar hemispheres, vermis and the flocculi, and forms part of the motor system that participates in post-natal sensorimotor functioning, particularly relating to classroom performance during foundation level learning once the child enters school. The flocculonodular lobe receives projections from the vestibular system (the sensory receptors in the middle

ear) and takes part in the control of balance and eye movements (Kolb and Whishaw 2003). Lesions to the midline areas of the cerebellum might disrupt balance, eye movements, upright posture and walking, but do not substantially disrupt other movements such as reaching, grasping and using the fingers (Kolb and Whishaw, 2003). It is thus suggested that attainment of developmental milestones, particularly crawling and walking, might be delayed due to hypo- and hypervitaminosis A during gestation. Sensorimotor learning during the early post-natal developmental years might thus be adversely affected, as summarised in TABLE II below.

Involvement in handwriting

Lesions to the lateral parts of the cerebellum disrupt arm, hand and finger movements, because of cerebellar involvement in the timing and accuracy of movements. According to Thatch *et al.*, (1992) the primary role of the cerebellum is to help make fine adjustments needed to keep movements accurate. In addition to an inability to maintain movement accuracy, the child's error restoration might also be impaired, suggesting that the child might manifest classroom behaviour such as repetitive erasure of faulty attempts, yet without noticeable

TABLE II
Possible sensorimotor learning deficits due to hypo- and hypervitaminosis A during gestation

Affected area	Learning deficits
Cerebellum	All forms of motor learning and vestibular functioning; Compromised movement-to-movement learning such as handwriting
Flocculonodular lobe	Poor static and dynamic balance; Eye movement deficits
Midline parts of the cerebellum	Disrupted balance, eye movements, upright posture and walking
Lateral parts of the cerebellum	Disrupted arm, hand and finger movements; Compromised timing and accuracy of movements; Inability to detect and restore errors of movement
Ganglion cell layer	Deficits in encoding of visual information; Faulty saccades and fixations; Compromised reading fluency and comprehension; Segmentation problems; Difficulty detecting the prosodic patterns of speech; Difficulty detecting syntactic or grammatical structures of speech; Faulty lip-reading; McGurk effect;
Suprachiasmatic nucleus (SCN)	Cortical energy balance dysregulation; Disturbed circadian rhythms; Altered mood and emotional processes; Defective arousal regulation; Altered attentional processes

improvement. Traditionally these types of difficulties were ascribed to inadequate fine motor control and lack of copying skills. However, writing and drawing partially depend on movement-to-movement learning and adjustments that are made by the cerebellum (Kolb and Whishaw, 2003). These authors explain error detection and restoration involved in handwriting as follows: Suppose a child performs a specific hand skill involved in letter formation, but finds that the shape is entirely incorrect. The child's next attempt is aimed at correcting the original error, resulting in two different versions of the same manoeuvre, i.e., the movement that the child intended to make, and the actual movement as recorded by sensory receptors in the fingers, arm and shoulder. If the first attempt at letter formation is successful, the child does not need to correct the next attempt; however, if the first attempt is incorrect, an adjustment is required. "One way in which the adjustment might be accomplished is through the feedback circuit that allows the cerebellum to correct movements. The cerebellum receives information about the instructions sent to the motor neurons by the inferior olivary nucleus. It receives information about the actual movement through the spinocerebellar tract. By comparing the message for the intended movement with the movement that was actually performed, the cerebellum can send an error message to the cortex to improve the accuracy of the subsequent movement" (Kolb and Whishaw, 2003). In keeping with this explanation, the cerebellum uses information about the intended movement as well as the actual movement to calculate the error and projects to the cortex how to correct the movement. Information about this correction is incorporated into the child's next attempt at letter formation.

The rhythm involved in handwriting might also be disrupted.

Involvement in vision

Retinal is also essential for normal vision (Thompson *et al.*, 1963; Olson, 1984; Chew, 1993; Blomhoff, 1994; Eskild and Hansson, 1994; Debier and Larondelle, 2005) and normal eye development (Clagett-Dame and DeLuca, 2002). Hypo- and hypervitaminosis A during gestation might result in constriction of the optic nerves, as well as atrophy and gliosis of the ganglion cell layer and the nerve fibre layer (van der Lugt and Prozesky, 1989). The ganglion cells send axons into the brain proper (the retina is considered to be part of the brain), thus playing a role in the retina's encoding of information (Kolb and Whishaw, 2003). Also, lesions to the midline areas of the cerebellum might disrupt eye movements needed for optimal vision. Encoding of visual information, as well as appropriate eye movements, play an important role in reading. Since eye movements are closely associated with saccades and fixations during any reading task, learning to read might be compromised. Saccades take 10 – 20 milliseconds to complete, and are separated by fixations lasting about 200 – 250 milliseconds. The length of each saccade is about eight letters or spaces, and information is extracted from the text only during each fixation, and not during the intervening saccades (Eysenck 2001). When the retina's encoding of information is already compromised due to hypo- and hypervitaminosis A, there would be an even further decline in extraction of information from the text during fixations. Without de-emphasising the impact of higher-level cognitive processes, it is suggested that if the perceptual span is compromised by

faulty eye movements, fixations would be defiant as well, and both reading fluency and reading comprehension might be compromised.

Involvement in auditory functioning

Hypo- and hypervitaminosis A during gestation may also result in auditory deficits, e.g. external ear defects and temporal bone abnormalities within the inner ear (de la Cruz *et al.*, 1984; Hansen and Pearl, 1985; Goulding and Pratt, 1986; Hendrickx and Hummler, 1992; Emmanouil-Nikoloussi *et al.*, 2000). The receptors in the inner ear detect differences in air pressure as changes in pitch, loudness, and timbre, and these differences in pressure are conveyed from the inner ear to the brain as action potentials. These action potentials are interpreted in areas of the cortex in the temporal lobe as sounds, language, and music. The auditory system is composed of tonotopic maps, and it locates sound in space by comparing the time of the sound's arrival at each ear, which is subject to the perception of the space around the body (Kolb and Whishaw, 2003). When perception of timing and length of an auditory stimulus is compromised, post-natal sound location might be compromised in a child that was exposed to hypo- or hypervitaminosis A during gestation, as a result of temporal bone abnormalities within the inner ear. The inner ear also contains the receptor system that mediates static and dynamic balance. Apart from cerebellar involvement in eye movement control, the pathways projected from the balance receptors to nuclei in the brainstem also aid in controlling eye movements (Kolb and Whishaw, 2003).

In addition, a child who suffers from disorders of the cerebellum might suffer a loss of timing, both in movement and

in perception (finger tapping, judging rhythm and the length of an auditory stimulus) (Kolb and Whishaw, 2003). This might manifest as poor time perception, e.g. embedded rhythm associated with speech sounds involved in language acquisition, awareness of syllables in words, difficulty memorising songs and poems, and these might easily be mistaken for temporal lobe lesions. Timing, rhythm and length of an auditory stimulus are closely linked to accurate perception of speech. Language is spoken at a rate of up to 12 phonemes per second, and one can understand speech at a rate of 50 to 60 sounds per second (Werker and Tees, 1992). Eysenck (2001) asserts, "speech typically consists of a continuously changing pattern of sound with few periods of silence." When the perception of the length of sounds and silences are disrupted, the child might find it difficult to decide how the continuous stream of sound should be divided up into words, in keeping with Eysenck's proposed "segmentation problem" (Eysenck, 2001). In addition, the child might have difficulty detecting the prosodic patterns of speech necessary for working out syntactic or grammatical structures. It is further suggested that synchronisation of visual and auditory information is closely related to the perception of timing, rhythm and length of auditory stimuli mediated by the cerebellum, and lip-reading might thus be compromised. Eysenck (2001) asserts that even individuals with normal hearing make use of visual information from lip movements to make sense of speech sounds. However, when perception of timing, rhythm and length of auditory stimuli is impaired, this might lead to the so-called McGurk effect (McGurk and MacDonald, 1976). McGurk and MacDonald demonstrated the importance of lip-reading by having someone repeating "ba" over and over again.

They then changed the sound channel to “ga” repeatedly in synchronisation with the lip movements still indicating “ba”. Their research participants reported that they heard “da”, which represented a blending of the visual and the auditory information. Green *et al.*, (1991) also found this McGurk effect even when there was a female face and a male voice involved, and they suggested that information about pitch becomes irrelevant early in speech processing. The McGurk effect thus refers to a mismatch between vision and hearing, implying impaired integration of speech information across sensory modality. This McGurk effect might easily be misdiagnosed as auditory discrimination difficulties.

Involvement in attentional and emotional processes

The cerebellum was long believed to simply control motor coordination, but it is now known to contribute to attentional and emotional processes as well (Heath *et al.*, 1980; Panksepp, 1998). Beside the ganglion cells that play a part in vision, some other specialised ganglion cells form the retinohypothalamic tract to the suprachiasmatic nucleus that play a role in regulating circadian rhythms. The suprachiasmatic nucleus (SCN) might be viewed as the “major pacemaker for the daily clock” (Panksepp, 1998), and is situated in the hypothalamus above the optic chiasm. The multiple output pathways from the SCN control practically all behavioural rhythms, from feeding and sleep to arousal and cortical energy balance regulation (Panksepp, 1998). In addition, circadian rhythms are thought to have some relationship to mood and emotional processes (Barlow and Durand, 2002). It thus follows that lesions to the

cerebellum and the SCN might result in defective arousal regulation, and it might happen that such a child is diagnosed with Attention-Deficit Disorder, predominantly inattentive type (American Psychiatric Association, 2000) and treated with methylphenidate (Ritalin), as opposed to administration of melatonin, which is widely used to treat circadian rhythm disturbances (Barlow and Durand, 2002).

Conclusion

It is thus concluded that during the period of early foetal development the supply of vitamin A must be carefully managed to ensure that the developing foetus is exposed to neither too little nor too much vitamin A, because either condition can have teratogenic consequences that may affect the midline and lateral parts of the cerebellum, floccular lobe, ganglionic cell layer as well as the suprachiasmatic nucleus of the brain. Changes in the functioning of these areas due to hypo- and hypervitaminosis A, may lead to developmental and learning disabilities involving all forms of motor learning, vestibular functioning, eye and visual system deficits, disrupted sleep rhythms as well as altered mood and emotional processes.

Summary

Supplementation during pregnancy forms a vital part of the well-being and development of the unborn child as well as the mother. Very often different brands of over-the-counter vitamins and minerals are taken, without considering the possibility of exceeding the maximum daily allowance, particularly where it concerns fat-soluble vitamins like vitamin

A. Although many people are aware of the consequences of taking too little vitamin A, this fat-soluble vitamin is stored in the body and over-dosage may occur when taking high doses. In this paper we investigate the effects of hypo- and hypervitaminosis A on craniofacial structures, lungs, hearts, limbs and the kidneys as well as the involvement in foetal nervous system development and post-natal sensorimotor functioning. Furthermore, we discuss how hypo- and hypervitaminosis A may affect the midline and lateral parts of the cerebellum, vermis, flocculi, ganglionic cell layer as well as the suprachiasmatic nucleus of the brain. Changes in the functioning of these areas due to hypo- and hypervitaminosis A, may lead to developmental and learning disabilities involving all forms of motor learning, vestibular functioning, eye and visual system deficits, disrupted sleep rhythms as well as altered mood and emotional processes.

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