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RESEARCH ARTICLE

RETINOL PALMITATE PREVENTS DEVELOPMENT OF FORELIMB IN MOUSE EMBRYO

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ABSTRACT

Vitamin-A is known for its effects on differentiation and morphogenesis during vertebrate development, as it is important for reproduction, Development and growth. Hypo and hyper vitaminosis-A both provoke epithelial pathologies in animals and human beings. So a critical value of vitamin-A is required in vivo for maintenance of normal architecture and functions of much body tissue. The pregnant female mice of one group were treated with a high dose 4IU/day/ 40gm body weight concentration of Retinol Palmitate (RP) by intubation from 10th day gestation to 15th day gestation. Another group was not given RP treatment serves as control group.

The treated mice delivered the externally malformed neonates on 19th day of gestation i.e.2 day earlier. Whereas control group delivered normal neonates on 21st day of gestation. The various external malformaties shown by the neonates of treated group like, absence of forelimb, reduced and without digits hind limb, and also absence of eye and ear.

INTRODUCTION

Vitamin-A refers to group of fat-soluble substances that are structurally related to and posses the biological activity of the parent substances of the group called all-trans retinal or retinol. Vitamin-A plays vital role in vision (Warkany[22]), epithelial differentiation, growth (Takahashi[17]), reproduction, pattern formation during embryogenesis, bone development(Tuiki[18]), haematopoisis, and brain development. It is also important for the maintenance of the proper functioning of the immune system.

Vitamin-A is not synthesized in the body, but it is derived from carotenes of plant origin β-carotenes is converted in to vitamin-A alcohol (Retinol) and is transported by blood to liver where it is esterifies and sores as vitamin-A palmitate. Retinol is most potent form when given exogenously.

Higher doses of retinoid produce terogenic effects such as retardation of general body growth, enlargement of heart and neural tube, disruption of skin, blood vessels are reduced in chick embryo at different development stages by different excess dose of retinoids (Singh[15]) Shobhawat [14] reported that RA influences the early process of chick development in a specific manner. Excess dose of RA produce abnormalities including brain vesicles, neural tube, notochord, eye and vascular system. RA also inhibits certain protein bands. Goulding and Prett [7] reported that when 8th day embryo is treated with higher concentration of retinoic acid solution, approximately 1/3 of the embryos developed a very specific pattern of anomalies, including Grammatik reduction in the size of 1st and 2nd pharyngeal arches. Kistler [10] reported that when RA (120mg/kg) administered orally to pregnant females on one of the 1st to 20th day of gestation and fetus were examined on 21st day of gestation. They observed that RA was highly embryo lethal when administered on 9th and 10th day of gestation (96.2% and 100% resumption).

Kistler observed several multiple defects produced by RA on 9th and 11th day of gestation, but specific malformations involving the axial skeleton and cleft palate retardation resulting from treatment on 12th –18th day of gestation.

Gosh *et al*.[5] reported that the active derivatives of vitamin A (retinoids) play important and multiple role in mammalian development and homeostasis.

They observed exhibited odema, abnormal stasis of maternal blood and signs of desorption of the endothelial layer of fetal vessels of mid late gestation period.

Gupta, A8 reported that excess retinoic acid cause skeleton malformation and teratogenic effects on the developing liver and heart of mice when the treatment is given on the particular day.

Juliana *et al*.[9] discussed the roles of vitamin A during human development and molecular mechanism controlling its biological effects; they concluded that vitamin A derived signals are very tightly controlled in time and space during development. Wang *et al*.[20] reported that cleft palate its one of the major malformation induced by retinoic acid in both rodents and human. Retinoic acid recepto are also teratologically important. They would have exhibit a pattern of expression in the embryo reflecting in some manner distinctive feature of teratogenesis. In addition to nuclear retinoic acid receptor, there is family of cytoplasm protein

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which binds retinal (RBP-I and RBP-II) with high affinity (11).

Boylen .[2] reported that RBAP-I inhibits the access of retinoic acid to the nuclear receptors and clearly plays an important role in maintaining low level of free retinoic acid in specific embryonic cells.

Retinoic acid excess, in the context of embryonic cells and tissue, can be defined as an amount which exceed the binding capacity of CRABP-I (Perez-1989) in cells that contain it, allowing ectopic activation of nuclear retinoic acid receptor and hence an abnormal pattern of gene expression.

In contrast; cell that contain CRABP-I are those, which are able to bind maternal and therefore have the potential, through the oxidation of retinal to have higher level of free retinoic acid than other cells.

Retinoic acid act as hormone to affects gene expression thereby influence numerous physiological process. This RA are transported to the nucleus of cell bond to cytoplasmic retinoic acid binding protein (CRABP) with the nucleus RA binds to retinoic acid receptor proteins (RAR –Retinoic acid receptor and RR –Retinoid receptor). Once bound retinoic acid to RAR and RR form RAR/ RR heterodimer, which bind to regulatory region of chromosome called retinoic response elements (RARE). Binding of RAR/ RR to RARE on gene influence their rate of transcription, thereby influencing the synthesis of certain proteins used throughout the body (Dolle[4], Yamagata[23]).Through the stimulation and inhibition of transcription of specific genes, retinoic acid plays a major role in cellular differentiation, the specialization of cells of highly specific physiological role effects attributed to hyper vitaminosis-A appear to result from its role in cellular differentiation Once bound to retinoic acid, RAR and RR from RAR/RR heterodimers, which bind to regulatory region Of the chromosomes called retinoic acid response elements (RARE). Binding of RAR/RR to RARE on gene influence their rate of transcription, thereby influencing the synthesis of certain proteins used throughout the body. Though the stimulation and inhibition of transcription of specific genes, retinoic acid plays a major role in cellular differentiation.

Most of the physiological effects attributed to hyper vitamin appear to result from its role in cellular differentiation. .

The experiments were carried out on *Swiss albino* mice. For this experiment total eight mice were taken with male female ratio of 1: 3. These were divided in two groups (each group containing three females and one male) both were kept together overnight for mating and in the morning presence of vaginal plug was taken as gestation day zero. One group was given a high dose of RP i.e. 4mg / day /40gm body weight from gestation day 10^{th} to 16^{th} continuously. This group was called as treated group and the other group, which was not given any treatment, severed as controlled group. Both the groups were observed till parturition.

The treated group delivered externally malformed fetus on 19^{th} day of gestation while control group delivered normal fetus on 21^{st} day of gestation.

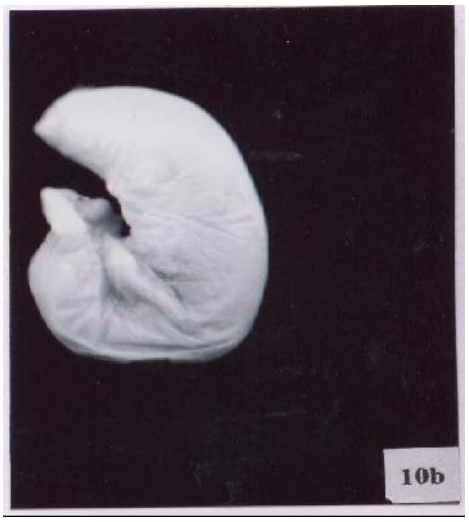
Significant malformations are

1. Absence of forelimbs and reduced hind limbs without digits.
2. Failure of development of eye and ear.

In mouse organ differentiation takes place during the critical period of 11^{th} -14^{th} day gestation. Thus, during this period hypovitaminosis-A as well as hypervitaminosis- A can cause malformation (Giroud[6], Warkany[21]). In the above said experiment dose of 4 IU/day /40gm body weight (normal requirement is 2.4 IU/day / 40gm body weight) was given during this critical period (Shenai[16]). Treated group also showed 2 day early parturition (Baker[1]) in mouse limb formation starts at11th day gestation, so higher dose of RP given from the 10^{th} day –15^{th} day of gestation prevented normal growth of fore limbs.

Similarly eye and ear buds are formed on 12^{th} day of gestation, which was also prevented due to excess dose of RP during this period.

Control 2X



Treated 2X

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