بسم الله الرحمن الرحيم

MONA MAGHRABY

شبكة المعلومات الجامعية

التوثيق الالكتروني والميكروفيلم

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جامعة عين شمس

التوثيق الإلكتروني والميكروفيلم

قسم

نقسم بالله العظيم أن المادة التي تم توثيقها وتسجيلها
علي هذه الأقراص المدمجة قد أعدت دون أية تغيرات

يجب أن

تحفظ هذه الأقراص المدمجة بعيدا عن الغبار

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Introduction

Neurulation and the subsequent growth and patterning of the neural tube is a very complex process (***Hansen et al., 2001***). Patterning of the growing neural tube occurs in both the rostro-caudal axis and the dorso-ventral axis under the influence of extracellular morphogens *(signaling proteins)* such as fibroblast growth factors ***(FGFs)***, *retinoic acid, Wnts, sonic hedgehog and bone morphogenetic proteins* ***(BMP)*** *(****Booth et al., 2005; Horland, 2003****)*. A role for Retinoic Acid ***(RA)*** in rostro-caudal patterning of the nervous system has been well established *(****Ikemi et al., 2001****)*. Recently, there is evidence that ***RA*** sets the dorsal, inter-neuron and ventral neuron boundaries within the rostral spinal cord.

Vitamin A and its derivatives ***(the retinoids)*** are essential for both normal embryonic development and maintenance of postnatal differentiation in the adults (***Hofmann and Eichele, 1994***).It is important in maintaining normal growth, proliferation and differentiation of epithelial tissues, and maintaining visual and reproductive functions ***(File et al, 1999)***. Retinoic acid is required during nervous system development for a series of inductive events. Firstly, it acts as a posteriorizing factor during neural induction along

with ***Wnts***and ***FGFs*** to pattern the anterior spinal cord ***(Greek et al, 1993)***. Also, it is required for the induction of a subset of inter-neurons known as ***V0*** and ***V1***. In addition, it is required for the induction of motor neural differentiation throughout the spinal cord via the gene ***NeuroM (Martinez et al., 2006)***.

Mark et al. 1995 found that insufficient vitamin A induces failure of growth, stoppage of embryonic segmentation and vascularization, with subsequent resorption of the embryo.

On the other hand, excess vitamin A results in teratogenic effect during embryogenesis and affection of the integrity of cell membranes.

Retinoic acid is a well-known teratogen when administered during pregnancy and one of its many effects is to induce neural tube defects ***(Colakoqlu and Kukner 2004)***. These defects include spina bifida, vascular damage, malformation of the notochord, distortion of the neural folds, cell death in the neural tube, delayed posterior neuropore closure and cell death in the hind gut endoderm and mesenchyme ***(Sevc et al., 2009).***

Functional and behavioral deficits in the offspring of animals exposed to maternal hypervitaminosis A have been documented. Cognitive and behavioral abnormalities were detected in rat offspring ***(Paniagua et al., 2008).***

The teratogenic effects of vitamin A were developmentally stage-dependent, treatment during the immediate post-implantation period resulted in anomalies of the sensory organs and the cardiovascular system, whereas exposure later in gestation resulted in limb and genitourinary defects ***(Abbott and Birnbaum, 2006).***

Aim of the Work

The present work was designed to investigate the postnatal structural changes induced by prenatal administration of therapeutic dose of retinoic acid (vitamin A) on the spinal cord of albino rats. These changes, if found, was to be compared to those caused by prenatal administration of a mega dose of vitamin A.

Spinal Cord

Anatomy and Histology

The spinal cord is the most important structure between the body and the brain. It extends from the foramen magnum where it is continuous with the medulla to the level of the first or second lumbar vertebrae. It is a vital link between the brain and the body, and from the body to the brain ***(Standring and Borley, 2008).***

The spinal cord is 40 to 50 cm long and 1 cm to 1.5 cm in diameter**.** . It is a cylindrical structure of nervous tissue composed of white and gray matter, is uniformly organized and is divided into four regions: cervical (C), thoracic (T), lumbar (L) and sacral (S), each of which is comprised of several segments***(Stare et al., 1992).***

Two enlargements of the spinal cord can be visualized: The cervical enlargement, which extends between C3 to T1; and the lumbar enlargements which extends between L1 to S2 ***(Snell, 2007).***

The cord is segmentally organized. Two consecutive rows of nerve roots emerge on each of its sides. These nerve roots join distally to form 31 pairs of **spinal nerves.** There

are 31 segments, defined by 31 pairs of nerves exiting the cord. These nerves are divided into 8 cervical, 12 thoracic, 5 lumbar, 5 sacral, and 1 coccygeal nerve ***(Snell, 2007).***

Dorsal and ventral roots enter and leave the vertebral column respectively through intervertebral foramen at the vertebral segments corresponding to the spinal segment. The spinal nerve contains motor and sensory nerve fibers to and from all parts of the body. Each spinal cord segment innervates a dermatome ***(Standring and Borley, 2008).***

The cord is sheathed in the same three meninges as is the brain: the pia, arachnoid and dura. The dura is the tough outer sheath, the arachnoid lies beneath it, and the pia closely adheres to the surface of the cord. The spinal cord is attached to the dura by a series of lateral denticulate ligaments emanating from the pial folds ***(Mulder et al., 2000).***

During the initial third month of embryonic development, the spinal cord extends the entire length of the vertebral canal and both grow at about the same rate. As development continues, the body and the vertebral column continue to grow at a much greater rate than the spinal cord proper. This results in displacement of the lower parts of the

spinal cord with relation to the vertebral column ***(Berkovitz et al., 2010).***

The outcome of this uneven growth is that the adult spinal cord extends to the level of the first or second lumbar vertebrae, and the nerves grow to exit through the same intervertebral foramina as they did during embryonic development. This growth of the nerve roots occurring within the vertebral canal, results in the lumbar, sacral, and coccygeal roots extending to their appropriate vertebral levels ***(You et al., 2005).***

Internal Structure of the Spinal Cord

A transverse section of the adult spinal cord shows white matter in the periphery, gray matter inside, and a tiny central canal filled with CSF at its center. Surrounding the canal is a single layer of cells, the ependymal layer. Surrounding the ependymal layer is the gray matter – a region containing cell bodies – shaped like the letter "H" or a "butterfly". The two "wings" of the butterfly are connected across the midline by the dorsal gray commissure and below the white commissure (***Standring and Borley, 2008).***

The shape and size of the gray matter varies according to spinal cord level. At the lower levels, the ratio between

gray matter and white matter is greater than in higher levels, mainly because lower levels contain less ascending and descending nerve fibers ***(Standring and Borley, 2008).***

A- Gray Matter

The gray matter mainly contains the cell bodies of neurons and glia and is divided into four main columns: dorsal horn, intermediate column, lateral horn and ventral horn column **.**The dorsal horn is found at all spinal cord levels and is comprised of sensory nuclei that receive and process incoming somatosensory information. From there, ascending projections emerge to transmit the sensory information to the midbrain and diencephalon. The intermediate column and the lateral horn comprise autonomic neurons innervating visceral and pelvic organs. The ventral horn comprises motor neurons that innervate skeletal muscle ***(Standring and Borley, 2008).***

A more recent classification of neurons within the gray matter is based on function. These cells are located at all levels of the spinal cord and are grouped into three main categories: root cells, column or tract cells and propriospinal cells ***(Snell, 2007).***

At all the levels of the spinal cord, nerve cells in the gray substance are multipolar, varying much in their morphology. Many of them are Golgi type I and Golgi type II nerve cells. The axons of Golgi type I are long and pass out of the gray matter into the ventral spinal roots or the fiber tracts of the white matter. The axons and dendrites of the Golgi type II cells are largely confined to the neighboring neurons in the gray matter ***(Standring and Borley, 2008).***

The root cells are situated in the ventral and lateral gray horns and vary greatly in size. The most prominent features of the root cells are large multipolar elements exceeding 25 μm of their somata. The root cells contribute their axons to the ventral roots of the spinal nerves and are grouped into two major divisions: 1) somatic efferent root neurons, which innervate the skeletal musculature; and 2) the visceral efferent root neurons, also called preganglionic autonomic axons, which send their axons to various autonomic ganglia ***(Standring and Borley, 2008).***

The column or tract cells and their processes are located mainly in the dorsal gray horn and are confined entirely within the CNS. The axons of the column cells form longitudinal ascending tracts that ascend in the white

columns and terminate upon neurons located rostrally in the brain stem, cerebellum or diencephalon. Some column cells send their axons up and down the cord to terminate in gray matter close to their origin and are known as intersegmental association column cells ***(Snell, 2007).***

Other column cell axons terminate within the segment in which they originate and are calledintrasegmental association column cells. Still other column cells send their axons across the midline to terminate in gray matter close to their origin and are called commissure association column cells ***(Ruhle et al., 2001).***

The propriospinal cells are spinal interneurons whose axons do not leave the spinal cord proper. Propriospinal cells account for about 90% of spinal neurons. Some of these fibers also are found around the margin of the gray matter of the cord and are collectively called the fasciculus proprius or the propriospinal or the archispinothalamic tract **.**

B- White Matter

Surrounding the gray matter is white matter containing myelinated and unmyelinated nerve fibers. These fibers conduct information up (ascending) or down (descending) the cord. The white matter is divided into the dorsal (or

posterior) column (or funiculus), lateral column and ventral (or anterior) column .

Three general nerve fiber types can be distinguished in the spinal cord white matter:

1) Long ascending nerve fibers originally from the column cells, which make synaptic connections to neurons in various brainstem nuclei, cerebellum and dorsal thalamus,
2) Long descending nerve fibers originating from the cerebral cortex and various brainstem nuclei to synapse within the different Rexed layers in the spinal cord gray matter.
3) Shorter nerve fibers interconnecting various spinal cord levels such as the fibers responsible for the coordination of flexor reflexes. Ascending tracts are found in all columns whereas descending tracts are found only in the lateral and the anterior columns ***(Standring and Borley, 2008).***

Blood Supply of the Spinal Cord

The arterial blood supply to the spinal cord in the upper cervical regions is derived from two branches of the vertebral arteries, the anterior spinal artery and the posterior spinal

arteries. At the level of medulla, the paired anterior spinal arteries join to form a single artery that lies in the anterior median fissure of the spinal cord ***(Pan and Baker, 2007).***

The posterior spinal arteries are paired and form an anastomotic chain over the posterior aspect of the spinal cord. A plexus of small arteries, the arterial vasocorona, on the surface of the cord constitutes an anastomotic connection between the anterior and posterior spinal arteries. This arrangement provides uninterrupted blood supplies along the entire length of the spinal cord ***(Standring and Borley, 2008).***

Development of the Spinal Cord

Neurulation is the process of forming the neural tube, which will become the brain and spinal cord. In humans, it begins in the 3rd week after fertilization**.**

At the end of the 2nd week (post fertilization), the embryo is a bilamminar disc consisting of epiblast cells in the top layer and hypoblast in the bottom layer. Soon, a groove, the primitive streak, appears in the caudal 3rd of the disc, signaling the initiation of gastrulation, the process of forming a trilamminar disc containing three germ layers- ectoderm, mesoderm, and endoderm ***(Scott et al., 2005).***