DOI: 10.55522/jmpas.v5i6.0101 ISSN NO. 2320 – 7418

International peer reviewed open access journal

Journal of Medical Pharmaceutical and Allied Sciences

Journal homepage: www.jmpas.com CODEN: JMPACO

Research article

Effect of sodium valproate in histological features of cerebellum in chick embryos

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Received – 20 October 2016**, Revised** - 25 November 2016, **Accepted** – 23 December 2016 **(DD-MM-YYYY)**

Refer This Article

Shabana Sultana, M A Doshi, N Jayasree, Mrudula Chandrupatla, 2016 Effect of sodium valproate in histological features of cerebellum in chick embryos. Journal of Medical, Pharmaceutical, and Allied Sciences, V 5 - I 6, Pages -386 – 388. Doi: https://doi.org/10.55522/jmpas.V5I6.0101.

ABSTRACT

Valproic acid is an antiepileptic drug prescribed as monotherapy in newly diagnosed cases of Epilepsy. It is also useful in combating generalized Tonic-Clonic Seizures, Partial Seizures, Myoclonic Seizures. It acts by increasing the levels of the Neurotransmitter GABA in the cerebrum. Valproate inhibits sustained repetitive firing induced by depolarization of cortical or spinal cord neurons. It produces small reductions of the low-threshold(T) Calcium current at clinically relevant but slightly higher concentrations then limit sustained repetitive firing. Reducing T currents may contribute to the effectiveness of Valproic acid against partial and tonic–clonic seizures and absence seizures respectively.

In vitro, Valproate can stimulate the activity of the GABA synthetic enzyme, Glutamic Acid Decarboxylase and inhibit GABA degradative enzymes, GABA trasaminases. But studies show that they cause defects in the formation of neural tube if used during pregnancy.

In the present study fertilized eggs were administered with Sodium Valproate at 24 hours of incubation and the development of Cerebellum was studied after 20 days. The histological and gross features of Cerebellum were identified.

Keywords: Sodium Valproate, Chick Embryo, Cerebellum.

INTRODUCTION

The study of the Cerebellum in Chick embryo (Gallus gallus) is very important because it controls physical activities, maintenance of the balance of the organism, regulation of muscle tone. The chick brain consists of three main parts cerebrum, cerebellum and medulla oblongata. The chick has large cerebral hemispheres and small cerebellar hemispheres. There are no significance differences that occur in the central nervous system of the birds compared to that mammal. The cerebral hemispheres were separated from cerebellum by a transverse fissure. The cerebellum in chick embryo of 20 days age consists of two components, gray matter and white matter. The gray matter is situated externally while the white matter is situated internally. Also cerebellum consists of cortex and medulla. The cortex consists of three layers molecular layer, purkinje cell layer and granular layer [1].

Considering the Anti-Epileptic Property of Sodium Valproate, the present study was undertaken to observe and elucidate the changes in the Cerebellum after administration of Drug. The changes were considered in relation to the anti- histogenesis or anti-mitotic activity of Sodium Valproate by administering the drug into Fertilized Eggs. An attempt has been made to observe if the Drug passes through Placental Barrier leading to Malformations of Foetus. Such a study will help in treating Epilepsy Patients who are Pregnant. Sodium Valproate has been experimented by few Scientists on Laboratory animals like Chick Embryos etc.and their observations were noted [2].

MATRIALS AND METHODS

Selection of eggs

Well developed, mature and healthy fertile eggs are selected from the breeders from white leg horn (gallus gallus). Excessively large or small eggs, cracked or thin shelled eggs are avoided because they will have difficulty in retaining moisture which is needed for proper chick development. Penetration of microorganisms increases in cracked eggs. Eggs should not be washed or wiped with clean cloth as it removes the protective coating and

promotes the entry of microorganism. Rubbing and washing also serves to force disease organisms through the pores of the shell.

Incubation of eggs

It was done for a period of 24 hours and 0.25ml of Sodium Valproate drug was injected, then the eggs were re incubated and sacrificed on 20 th day. The temperature should be 101 ° F for first week 102° F for second week 103° F for third week. Optimum growth for most of the species requires a relative humidity of 60% until eggs begin to pip, after which the relative humidity should be raised to 70%. The humidity is maintained inside the incubator by placing an open pan of water with suspending a piece of cloth from the water, proving wick action [3].

Administration of teratogenic agents in to intact chick embryo

Five eggs

were kept as control and Sodium Valproate was injected into other set of five experimental eggs. A small hole over the broad end of the experimental egg was made using 22-gauge needle.

0.25 ml of Sodium Valproate was injected into the egg after 48 hours of incubation. It was done with an insulin syringe. Following drug administration, the holes were sealed with molten wax after which the eggs were placed back into the incubator.

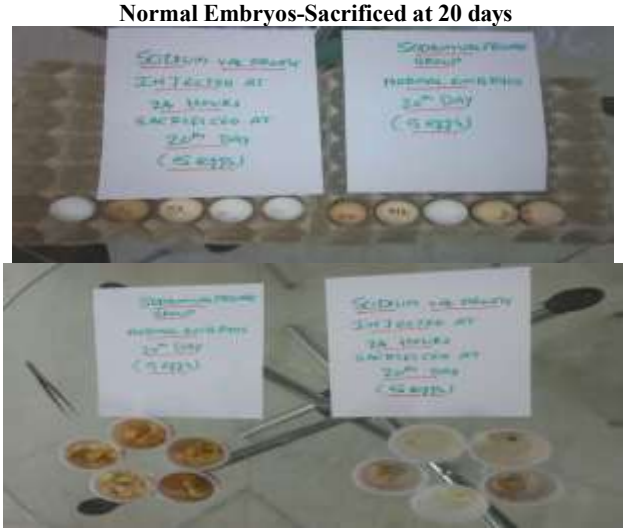
Processing and staining

After 20 days of incubation the eggs are broken and the embryo is collected and fixed in 10% formalin solution for 48 hrs. The cerebellum tissue is separated, processed and stained with Hematoxylin and eosin stains. The slides are studied under the simple microscope and various features are identified [4, 5].

RESULTS

Sodium Valproate administration resulted in a dose dependent massive reduction in number of cells in all layers of cerebellum as compared to the number of cells of cerebellum from control. Sodium Valproate induced cytotoxicity was presented by reduction of cell-cycle resulted in an overall decrease of multiplication activity of nervous tissue. It was clearly associated with reduction of number of cells in all layers of cerebellum [6-7].

Normal Embryos-Sacrificed at 20 days



Sodium Valproate injected at 24 hours and sacrificed at 20 days

DISCUSION

Sodium Valproate has most influence on organogenesis stage of development where organs follow a distinct sequence of cell division, migration differentiation and cell death. The drug causes oxidative stress leading to apoptosis. Most frequently results in the failure of the neural tube closure (spina bifida) and may lead to reduced post-natal cognitive function in addition to major congenital malformations.

The normal chick embryo has shown devastating changes after the administration of Sodium Valproate.The drug administration resulted in a dose dependent massive reduction in the cells of all the layers of cerebrum as compared to the number from control. Sodium Valproate induced cytotoxicity manifested by dose dependent disturbance of cell-cycle resulted in an overall depression of proliferation activity clearly associated with the occurrence of malformations and embryonic death. The histological study of normal chick embryo brain- cerebellum tissue was compared with the drug administered chick embryo brain-cerebellum tissue at same age, which

showed a gross loss in cellularity.

The loss in the cellularity could be attributed to two factors

a decrease in proliferation of brain cells and induction of cell death in the brain cells of drug treated embryos. The results of the present study corroborate both the possibilities. Cerebellum obtained from sodium valproate treated foetuses upon incubation in vitro showed a decreased proliferative ability (cell number) as compared to cerebellar cells of untreated fetuses. Sodium Valproate produced dose-related Teratogenic effects. The brain cells of foetuses obtained from Sodium Valproate treated mice showed an increased population of cells with typical apoptotic morphology.

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