EFFECT OF SODIUM VALPROATE ON THE STRUCTURE OF THE PANCREAS AND THE TESTIS OF ALBINO RAT

THESIS

SUBMITTED FOR PARTIAL FULFILMENT
OF M.D. DEGREE
IN

HISTOLOGY

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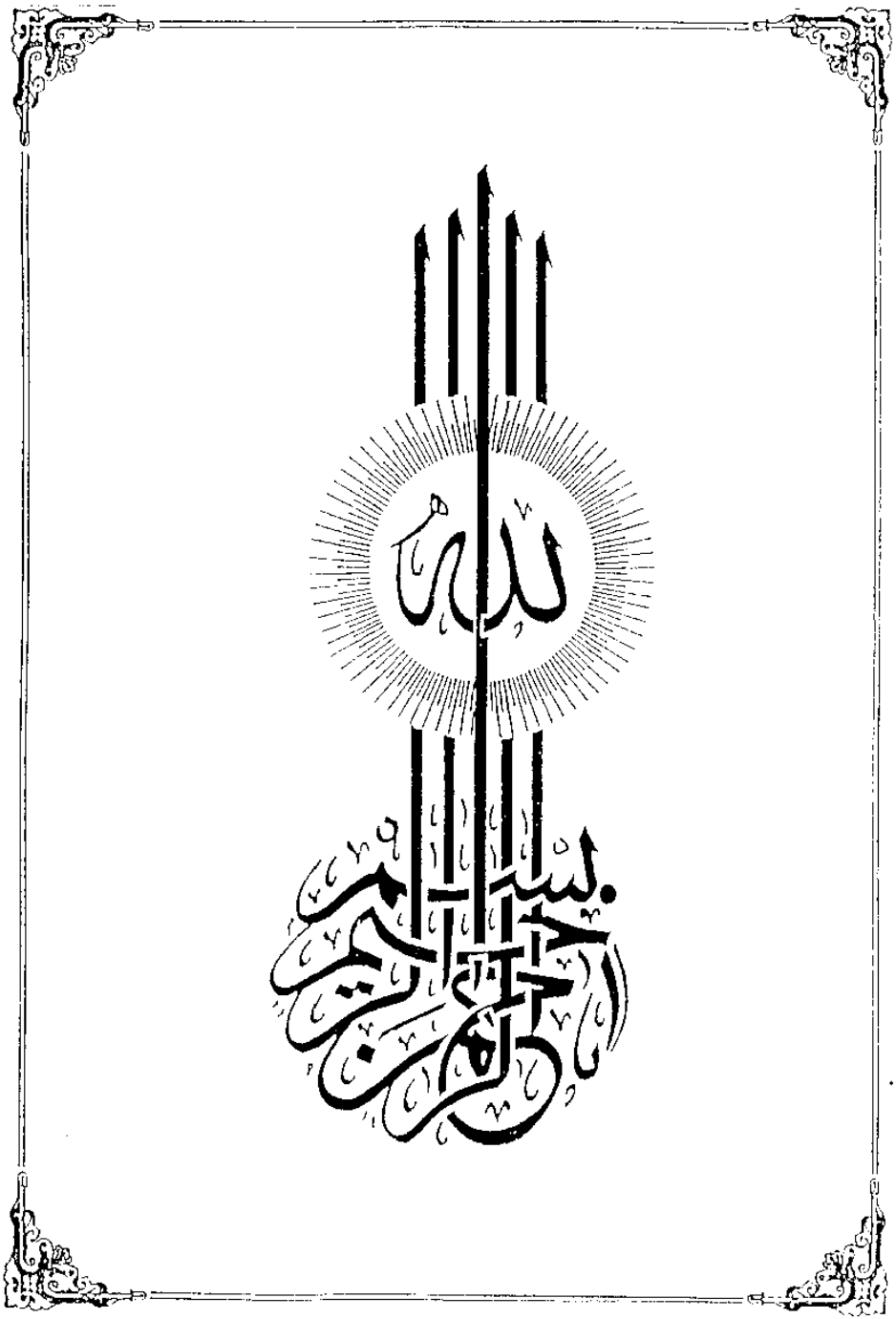
1995

To The Soul of My Father



INTRODUCTION AND AIM OF THE WORK

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Convulsive seizures are relatively common especially in children. Effective control of seizures can substantially reduce social as well as educational handicaps of epilepsy .

It is well known that the selection of the proper anticonvulsant greatly depends on the effeciency in the control of seizures and the frequency as well as the severity of the adverse reactions of the antiepileptic drug.

Rimmer and Richens (1985) stated that sodium valproate (valproate) is a remarkably safe and effective antiepileptic drug that is widely used in the treatment of epilepsy in both adults and children. It is well tolerated apart from the rare serious idiosyncratic adverse reactions.

Velten, Herzog and Muller (1990) stated that Valproate had by far the lowest potential to generate direct inhibition on the testicular endocrine system as compared to the other anticonvulsants.

Meanwhile, ***Walker, Smith, Barsoum and Macallum (1990)*** reported that testicular atrophy was observed in rats which received sodium valproate or calcium valproate at a dose of 1200-1600 mg/kg for 13 weeks. They added that in Beagle dogs given calcium valproate, atrophy in the testis was observed at a dose of 400 mg/kg for 13 weeks.

On the contrary either forms of valproate did not appear to exert any effect on the testis of the mice even at higher doses.

The same investigators noticed the development of dose dependent increased incidence and severity of atrophic pancreatitis in rats which received the anticonvulsant calcium valproate at doses of 250-500 mg/kg for 52 weeks. They suggested that calcium valproate had a toxicity profile similar to other forms of valproate namely valproic acid and sodium valproate.

On the other hand ***Parker, Helink, Ghishan and Greene (1981)*** mentioned that there was a poor correlation between valproate dosage or duration of therapy and the development of pancreatitis in treated epileptic patients.

Ford, Portman and Lum (1990) reported the occurrence of acute pancreatitis in four children treated with maintenance dialysis, while receiving valproic acid for the treatment of chronic seizures disorders. Since pancreatitis is a knowm complication of end stage renal failure, so the effect of valproate on the pancreas needs further investigation.

It is obvious that there is a lot of controversy about the actual effect of valproate on either the testis or the pancreas. So the aim of the present work is to clarify the effect of sodium valproate on the structure of the testis and the pancreas of albino rat. This may help the physicians who prescribe valproate to pay more attention for the drug potentially dangerous complication.

REVIEW OF LITERATURE

SODIUM VALPROATE

Sodium valproate (valproate) is a widely used anticonvulsant drug that has been used in treatment of various types of epilepsy. However it has been incriminated in some rare cases of severe adverse reactions.

Batalden, Van Dyne and Cloyd (1979) stated that valproic acid is a short chain fatty acid that seemed to be a relatively safe drug as compared to other anticonvulsants.

Available observation was postulated by ***Ferrandes and Eymard (1979)*** who mentioned that the metabolism of valproate in rat appeared to be similar to that in man.

Wade, Reynolds and Prusad (1982) emphasized that valproate is metabolized in the liver and is completely excreted in urine almost entirely in the form of its metabolites. It is extensively bound to plasma proteins and can cross both the blood brain barrier and the placental barrier. They added that valproic acid is a widely used anticonvulsant that can be administered as its sodium salt or as the acid itself.

Gram and Bensten (1983) suggested that the severe serious adverse reactions which might complicate valproate therapy seemed to be due to sudden metabolic aberration which resulted in the formation of toxic metabolites, so one may suffer from acute pancreatitis or acute hepatic toxicity while receiving valproate therapy.

Jeavons (1983) reported the superiority of a single daily dose over the repeated doses while receiving valproate as an anticonvulsant. This is because valproate unlike other anticonvulsants has a remarkable delayed effect.

Rimmer and Richens (1985) supported the previous idea, and added that the single daily dose had been proved to increase the effeciency of the drug without any tendency to increase the toxic effect. So they advised to use a single daily dose instead of a divided dosing schedule.

Vining (1987) mentioned that while anticonvulsants were incriminated in cognitive dysfunction of the treated epileptic patients, valproate appeared to have minimal effect on cognition.

Mechanism of Action of Valproate

Although much energy had been expended to elucidate the mechanism of action of valproate, it remains obscure till now. Non of the several hypothesis for its mechanism of action were adequately supported by experimental data.

Meldrum (1978) came to the conclusion that valproate might exert its effect via the elevation of the central concentration of the inhibitory neurotransmitter GABA, due to its inhibitory effect on certain enzymes in the GABA degradative pathway.

However, ***Loscher and Frey (1979)*** emphasized that valproate might increase central GABA concentration via the activation of the major synthetic enzyme glutamic acid decarboxylase.

Valproate might selectively enhance the postsynaptic GABA responses as postulated by ***MacDonald and Bergey (1979).***

On the other hand ***Salter and Johnston (1979)*** stated that the anticonvulsant effect of valproate might be mediated via the direct effect of the drug on the neural membrane, via an increase in membrane conduction to potassium ions, leading to an increase in the resting membrane potential.

Another hypothesis was accepted by ***Chapman, Riley and Meldrum (1981)*** who thought that valproate might exert an inhibitory effect on the excitatory amino acid transmitter aspartate, hence it reduced the central excitatory transmission.

Later on ***Chapman, Meldrum and Mendes (1983)*** denied any increase in GABA brain level following administration of valproate. They mentioned that some structural analogue of valproate with anticonvulsant activity did not raise brain GABA level.

However ***Johnston (1984)*** attributed the potentiating effect of valproate on GABA mediated neurotransmission in the CNS to either via inhibition of GABA degradation or via excitatory direct effect on pre and post synaptic GABA receptors. He added that GABA actually

modulated the hormonal secretion by acting on hypothalamic or pituitary levels or at both levels.

Finally ***Reynolds (1994)*** mentioned that the mechanism by which valproate exerted its anticonvulsant effect had not been yet understood. However he greatly supported the idea that valproate might increase the concentration of the inhibitory neurotransmitter GABA in the brain.

The Testis

Histology and Histochemistry of the Testis

The histological and the histochemical profile of the mammalian testis has been a matter of a lot of research work by many investigators.

Kabat and Furth (1941) performed a study on the distribution of the enzyme alkaline phosphatase in various human tissues. They emphasized that a moderate enzymatic reaction could be detected in the basement membrane of the seminiferous tubules of the testis while a diffuse weak reaction was observed in most of the spermatogenic cells. The blood capillaries also exhibited a strong enzymatic reaction.

Later on ***Bourne (1943)*** reported a moderate alkaline phosphatase activity in the interstitial tissue of the adult human testis . He added that all chromosomes in the germ cells undergoing maturation division gave also somesort of positive reaction.

Elfetman (1950) investigated the kinetics of spermatogenesis in rat and mentioned that as one generation of spermatozoa left the sertoli cells, its branches enclosed the next generation of spermatids in a cytoplasmic network.

Lynch and Scott (1951) studied the distribution of lipids in the testicular tissue of the adult albino rat. They found that lipids were restricted to the seminiferous tubules, occupying a position either at the basement membrane or in the luminal portion of the tubules. This difference was related to the maturation of the spermatogenic cells.They

thought that lipids were situated entirely in Sertoli cells, and moved in conjunction with the cyclic changes of spermatogenic epithelium.

In contrast to the above finding ***Long and Engle (1952)*** mentioned that lipids were also detected in the interstitial tissue of human testis in both the fibrous and polygonal types of cells. This was accompanied by a noticeable amount of the enzyme lipase which might be an indicative of active lipid metabolism of such cells . In the Sertoli cells of the normal tubules the author observed fine lipid droplets, whereas in fibrotic degenerated tubules of sterile patients the Sertoli lipids were increased greatly, both in size as well as in amount.

A study on the distribution of glycogen in adult human testis was also carried out by the same investigators. Glycogen was observed in Sertoli cells, spermatogonia and early primary spermatocytes, but not in the mature primary spermatocytes and the more mature cells.

The same pattern of glycogen distribution in the normal adult human testis was described by ***Mancini, Nolazco and DE LA Balze (1952)*** . They could also identify a weak alkaline phosphatase reaction in the Sertoli cells as compared to the intense reaction of the basement membrane of the seminiferous tubules and all the germ cells. They added that the intertubular connective tissue contained glycoproteins, rare collagen fibres and a dense net of reticular fibres surrounding the Leydig cells.

On the other hand, ***Montagna (1952)*** mentioned that whereas a noticeable amount of glycogen could be observed in Sertoli cells, spermatogonia, as well as small primary spermatocytes, yet the

spermatid and the interstitial cells were more or less devoid of glycogen. As regards the alkaline phosphatase enzymatic activity, he described an intense reaction in the interstitial tissue, the endothelial cells and the nuclei of the germ cells, while occasional Leydig cells exhibited weak to moderate reaction.

Padykula (1952) demonstrated the distribution of the succinic dehydrogenase enzyme in different tissues of the rat. He came to the conclusion that this enzyme was distributed in almost all tissues, being firmly attached within the cells, quite probably to the mitochondria.

A similar study was also performed by ***Nachlas, Tsou and DE Souza (1957)*** who implied that the succinic dehydrogenase enzyme was regularly observed in the cytoplasmic organelles. While moderate activity was observed in the germinal epithelium of the testis, the spermatozoa revealed a strong reaction. Meanwhile some spermatozoa did not stain at all.

Later on ***Hitzeman (1962)*** observed that the distribution of the enzyme succinic dehydrogenase in the testis of the mouse, achieved maximum intensity after puberty. They added that succinic dehydrogenase activity was particularly difficult to demonstrate adequately in Leydig cells of mouse testis. Furthermore, the same investigator suggested that steroid synthesis in the individual Leydig cells was unsynchronized.

However ***Turpeinen, Turpeinen and Talanti (1962)*** implied

that the enzyme succinic dehydrogenase was concentrated in both spermatozoa and Sertoli cells, while the interstitial cells exhibited moderate activity.

George and Ambadkar (1963) could localize lipase activity both in interstitium as well as in the germinal epithelium of rat testis. They noticed that as spermatogenesis proceeded, there was redistribution of the lipase enzyme from the periphery of seminiferous tubules to the lumina. The lipid followed the same pattern of distribution as that of the lipase and they played a definite role in the process of spermatogenesis.

Tice and Barrnett (1963) studied the ultrastructural distribution of different phosphatases in rat testis. They reported the presence of acid phosphatase activity in the dense bodies of Sertoli cells and within the Golgi apparatus of all spermatogenic cells.

On the other hand ***Kormano, Harkonen and Kontinen (1964)*** stated that both Leydig cells as well as all spermatogenic epithelium exhibited a moderate activity for the enzyme succinic dehydrogenase. A rapid decrease in this activity was observed in atrophied seminiferous tubules following experimental cryptorchidism in rat.

Further investigation on the histochemistry of the rat testis had been carried out by ***Niemi and Kormano (1965).*** They mentioned that there was apparent increase in the amount of lipids and the intensity of acid phosphatase activity in the cytoplasm of the developing spermatid as the cycle of the seminiferous epithelium progressed, reaching a maximum in mature sperms. Most of the lipids together with