Chapter 3

Effect of Picrotoxin-induced Epileptic Condition and Antiepileptic Drug Treatment on Rat Brain Mitochondrial ATPase Kinetics Properties

Introduction

The principle function of the mitochondrion is to produce energy in the form of ATP, which is achieved via the pyruvate dehydrogenase complex, citrate cycle, β-oxidation, respiratory chain and oxidative phosphorylation (1-3). Electron transport chain (ETC) releases energy (complex I to IV) which is used to pump protons out of the mitochondrial inner membrane. The potential energy stored in electrochemical gradient is used to condense ADP and P_i to generate ATP via complex V (ATP synthase), driven by the movement of protons back through a complex V proton channel i.e. F_oF_1ATPase (3, 4)

In earlier chapter it was shown that PTX-induced seizures adversely affected the oxidative phosphorylation in rat brain and liver mitochondria as well as mitochondrial F_oF_1ATPase activity (Chapter 2). Depletion of energy metabolites (ATP and phosphocreatine) is associated with seizure induced neuronal injury (5). Almost all intracellular ATP is known to be generated in the mitochondria and about one-third of the cellular adenine nucleotides are located in this organelle (6). Therefore, insults causing mitochondrial damage/dysfunction cause depletion of ATP, and excessive generation of ROS (7-11).

Hence, it was of interest to find out that what will be the effect of PTX-induced epileptic condition on the kinetic properties of F_oF_1ATPase in brain mitochondria. Further, studies were also carried out to decipher the possible effects of antiepileptic drugs viz.

Carbamazepine (CBZ), Lamotrigine (LTG) and Clobazam (CLB) in control and epileptic animals. The results of these investigations are summarized in this chapter.

Materials and Methods

Chemicals

Picrotoxin (PTX), ATP and bovine serum albumin (BSA) were purchased from Sigma Chemical Co. (St. Louis, USA). 2,4-dinitrophenol (DNP) was purchased from British Drug Houses (Dorset, Poole, England). All other chemicals were purchased locally and were of analytical-reagent grade.

CBZ, LTG and CLB (pure compounds) were generous gifts from Sarabhai Piramal Pharmaciuticals Ltd., Vadodara; Glaxo Smith Kline, UK and Aventis Pharma Ltd., Mumbai respectively.

Animals and treatments

Male albino rats of Charles-Foster strain weighing between 200-250g were used for the study. The animals had free access to food and water.

Induction of epileptic condition by PTX treatment was essentially the same as described in Chapter 2.

Treatment with AEDs

The three AEDs used in the present studies were insoluble in aqueous medium and hence were dissolved in propylene glycol. The AED treatment was given to two groups of animals:

I. **AED treatment to intact non-epileptic animals:**

The rats received intraperitoneal (i.p.) injections of AEDs at the doses of: CBZ, 25mg/kg body weight (12); LTG, 15mg/kg body weight (13, 14) and CLB, 10 mg/kg body weight (15) for 7 days. The controls received equivalent volume of propylene glycol (PG).

II. **AED treatment to PTX induced epileptic animals:**

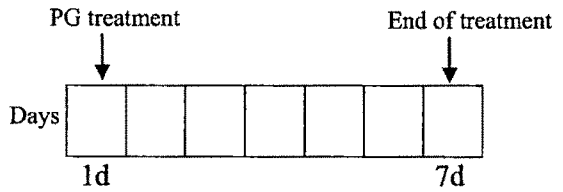
PTX treated animals were divided into three groups on the 14th day of the treatment. Three AEDs (CBZ, LTG and CLB) were given respectively to each group. AEDs were suspended in propylene glycol and the treatment was given i.p. 30 min prior to the PTX treatment. The doses were same as above. Thus, from the day 14 onwards, animals received AED treatment followed by PTX treatment for 7 consecutive days till the day 20, in each group (designated as PTX-CBZ, PTX-LTG and PTX-CLB). The control animals, either intact controls or the epileptic controls received equivalent volume of propylene glycol (PG).

Details of study design are represented below.

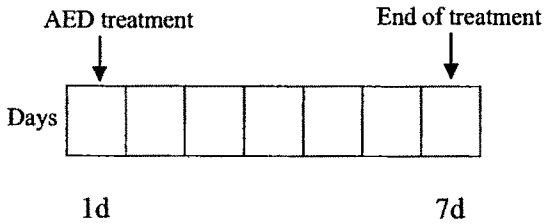
STUDY DESIGN

Schematic diagram of the study design. Four experimental groups were included in the study

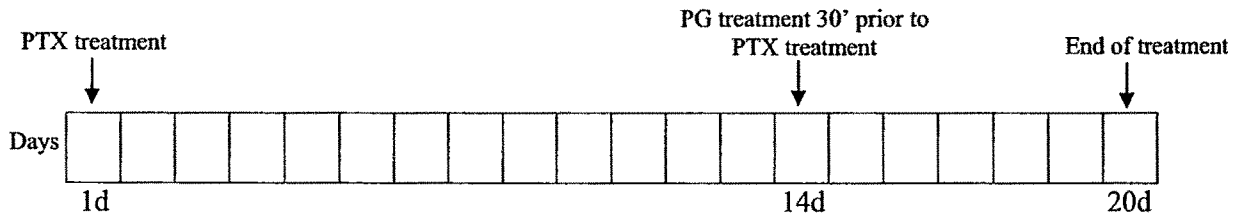
(1) Control animals



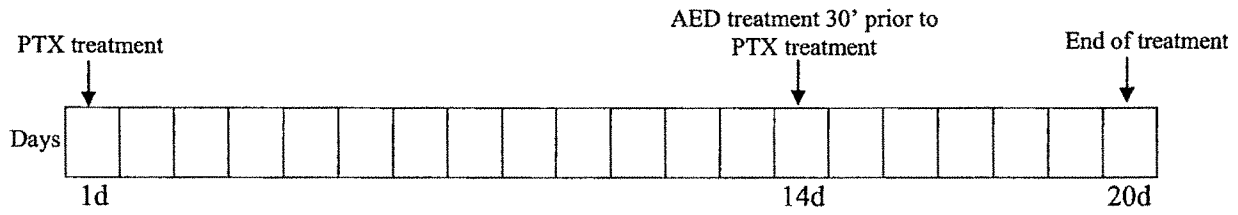
(2) AED treatment to control (non-epileptic) animals



(3) Epileptic animals treated with vehicle propylene glycol PG (Epileptic control)



(4) Epileptic animals treated with AEDs



The animals were killed by decapitation after the end of treatment period (i.e. on the day 8th after AEDs treatment and day 21st after PTX or PTX-AEDs treatment). Isolation of mitochondria was followed as described in Chapter 2.

Assay of ATPase

ATPase activity was measured in the assay medium (total volume 0.1 ml) containing 250 mM sucrose, 10 mM Tris-HCl buffer, pH 7.4, 10 mM KCl, 0.2 mM EDTA. The assays were performed in the absence and presence of $MgCl_2$ (2 mM) and DNP (50 μM), or a combination thereof. After pre-incubating the mitochondrial protein (Ca. 50-70 μg) in the assay medium at 37 °C, the reaction was initiated by addition of ATP at a final concentration of 2 mM. The reaction was carried out for 10 min and then terminated by the addition of 1.1 ml of 5% (w/v) trichloroacetic acid (TCA). The amount of liberated inorganic phosphorous was estimated by the method of Katewa and Katyare (2003) (16).

Substrate and temperature kinetics

The kinetics studies were carried out in the assay medium described above containing both Mg^{2+} and DNP. For substrate kinetics studies, the concentration of ATP was varied from 0.04 to 2 mM.

The temperature dependence of the enzyme activity was measured in the presence of fixed substrate concentration at 2 mM and the temperature was varied from 5 to 53 °C (4 °C steps).

Analysis of substrate kinetics data for determination of Km and Vmax was done by the Lineweaver-Burk and Eadie-Hofstee methods (17). The values of Km and Vmax obtained by both the methods were in close agreement and were averaged.

For the temperature kinetics data the determination of energies of activation for the high and low temperature ranges (E1 and E2, respectively) and phase transition temperature (Tt) were calculated form the Arrhenius plots (18).

Analyses of the data were carried out by employing Sigma Plot, version 5.0 (19), Microsoft Excel XP and Prism version 3.0.

Protein estimation was done by the method of Lowry *et al.* (1951) with BSA as the standard (20).

Results are given as mean ± SEM. Statistical evaluation of the data was performed using the Students' *t*-test.

Results and Discussion

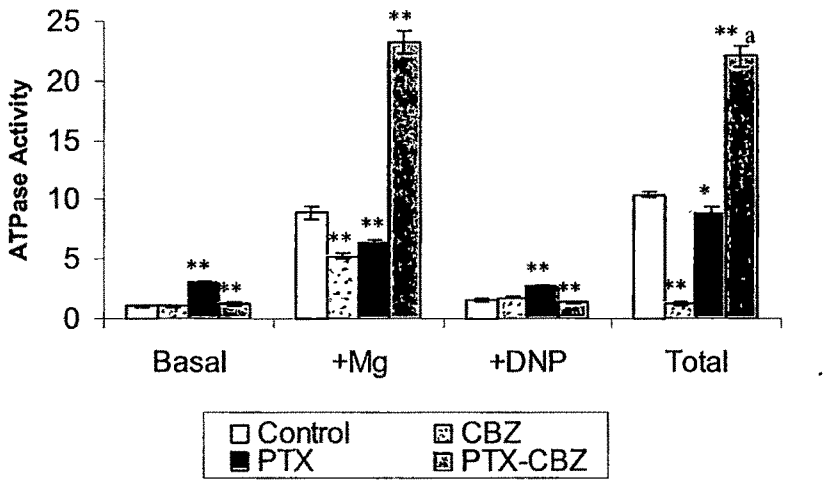
As it was evident from Figure 1 (Chapter 2) that PTX-induced convulsions caused elevation of basal and DNP stimulated activities, whereas Mg^{2+} stimulated activity was lower. Hence, the total activity (+Mg^{2+} and +DNP) was decreased.

CBZ treatment to the control animals significantly decreased Mg^{2+} stimulated activity (41% decrease) without altering basal and DNP stimulated activities (Fig 1). Consequently, the total activity decreased by 46%. LTG treatment to the control animals showed opposite effect where basal and DNP stimulated ATPase activity increased by 23 to 25% without altering Mg^{2+} stimulated and total activities, indicating increased mitochondrial membrane fragility (Fig 2). CLB treatment followed same pattern as CBZ but effect was marginal (Fig 3). Thus, AEDs treatment to the control animals differentially alters the mitochondrial ATPase activity.

CBZ treatment to PTX-induced epileptic animals restored the basal and DNP stimulated ATPase activities that were elevated in the epileptic condition, in contrast 1.5 fold elevation of Mg^{2+} stimulated activity was observed (Fig 1). LTG treatment to the epileptic animals decreased the basal and DNP activities as compared to PTX treated group, thus brings it back to the control level (Fig 2). CLB treatment followed the same pattern as CBZ group but significant increase in Mg^{2+} stimulated and total activity was observed as compared with control and PTX treated groups (Fig 3).

In general, when epileptic animals were treated with AEDs; all the three AEDs decreased basal and DNP-stimulated activity (21-57% decrease), that was found to be elevated in epileptic condition (Fig 1, Chapter 2). CBZ and CLB treatment lead to elevation of Mg^{2+} stimulated and total activity in the epileptic animals (Fig 1 and 3) which indicated increased membrane permeability. On other hand, LTG treatment was able to restore ATPase activity to the normality (Fig 2).

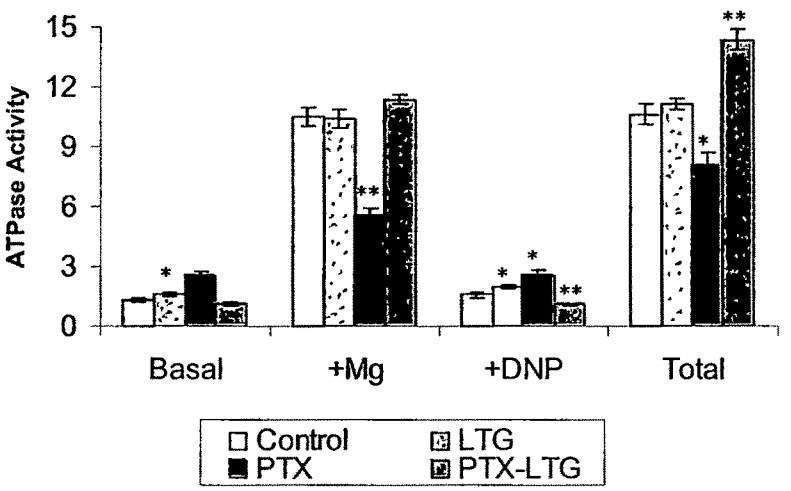
Figure 1. Effect of Carbamazepine (CBZ) treatment on brain mitochondrial ATPase activity in Control and PTX-induced epileptic condition



The experimental conditions are as described in text. The results are given as mean ± SEM of 8 independent observations. The ATPase activity is given in µmole P_i liberated /h/mg protein.

*, $p<0.02$ and **, $p<0.001$ compared with control.
a, $p<0.001$ compared with PTX treated group.

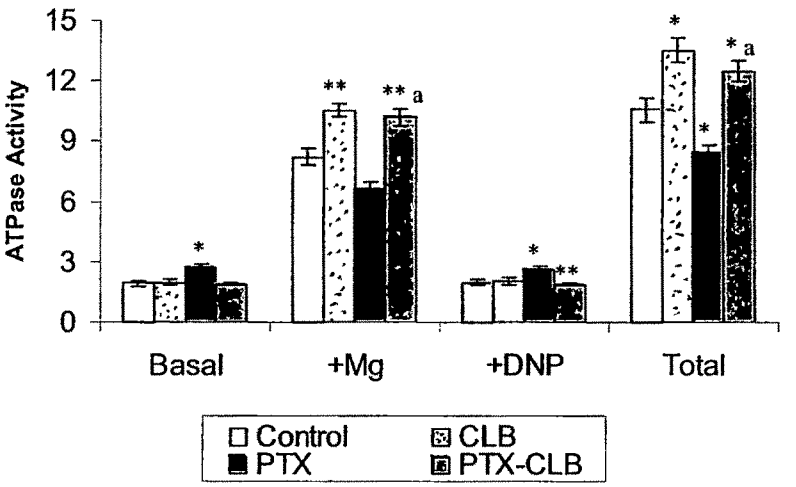
Figure 2. Effect of Lamotrigine (LTG) treatment on brain mitochondrial ATPase activity in Control and PTX-induced epileptic condition



The experimental conditions are as described in text. The results are given as mean ± SEM of 8 independent observations. The ATPase activity is given in µmole P_i liberated /h/mg protein.

*, $p<0.05$ and **, $p<0.001$ compared with control.

Figure 3. Effect of CLB (Clobazam) treatment on brain mitochondrial ATPase activity in Control and PTX-induced epileptic condition



The experimental conditions are as described in text. The results are given as mean ± SEM of 8 independent observations. The ATPase activity is given in μmole P_i liberated /h/mg protein.

*, $p<0.02$ and **, $p<0.001$ compared with control.
a, $p<0.001$ compared with PTX treated group.

In the next series of experiments the dependence of the enzyme activity on substrate i.e. ATP concentration was monitored. The results on effects of PTX-induced epileptic condition and effect of AED treatment on non-epileptic control and epileptic animals are shown in Fig 4 to 9. The substrate saturation curves for the control and treatment groups are shown in Fig 4 to 6. It is evident that typical substrate saturation patterns were obtained for the control and treatment groups.

The data were then analyzed in terms of Lineweaver-Burk and Eadie-Hofstee methods (17). For the sake of brevity only the corresponding Eadie-Hofstee plots are shown in Fig 7 to 9. In controls as well as the treatment groups the mitochondrial ATPase activity could be resolved into two kinetic components. Component I had low Km and Vmax, while the opposite was true for component II. The calculated values of Km and Vmax from the Lineweaver-Burk and Eadie-Hofstee plots were in close agreement, thus averages of the pooled values are given in Table 1. It is evident that in the epileptic animals the Vmax for component I was lower by 35% with a corresponding 36% decrease in Km. While in the case of component II, the Km values were about 2 fold higher.

In general CBZ, LTG and CLB treatment to the control animals lead to 1.3 to 2.6 fold increase in Km and Vm for kinetic component I (Table 2- 4). In contrast, disproportionate decrease in Km and Vm for component II was observed after AEDs treatment.

Figure 4. Typical substrate saturation curves for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with CBZ and epileptic treated with CBZ (PTX-CBZ) animals. The experimental details are as given in the text. Concentration of ATP was in the range of 0.04-2 mM. The abscissa represents the reaction velocity v, while the ordinate represents [S]. Reaction velocity is in μmol Pi liberated/h/mg protein.

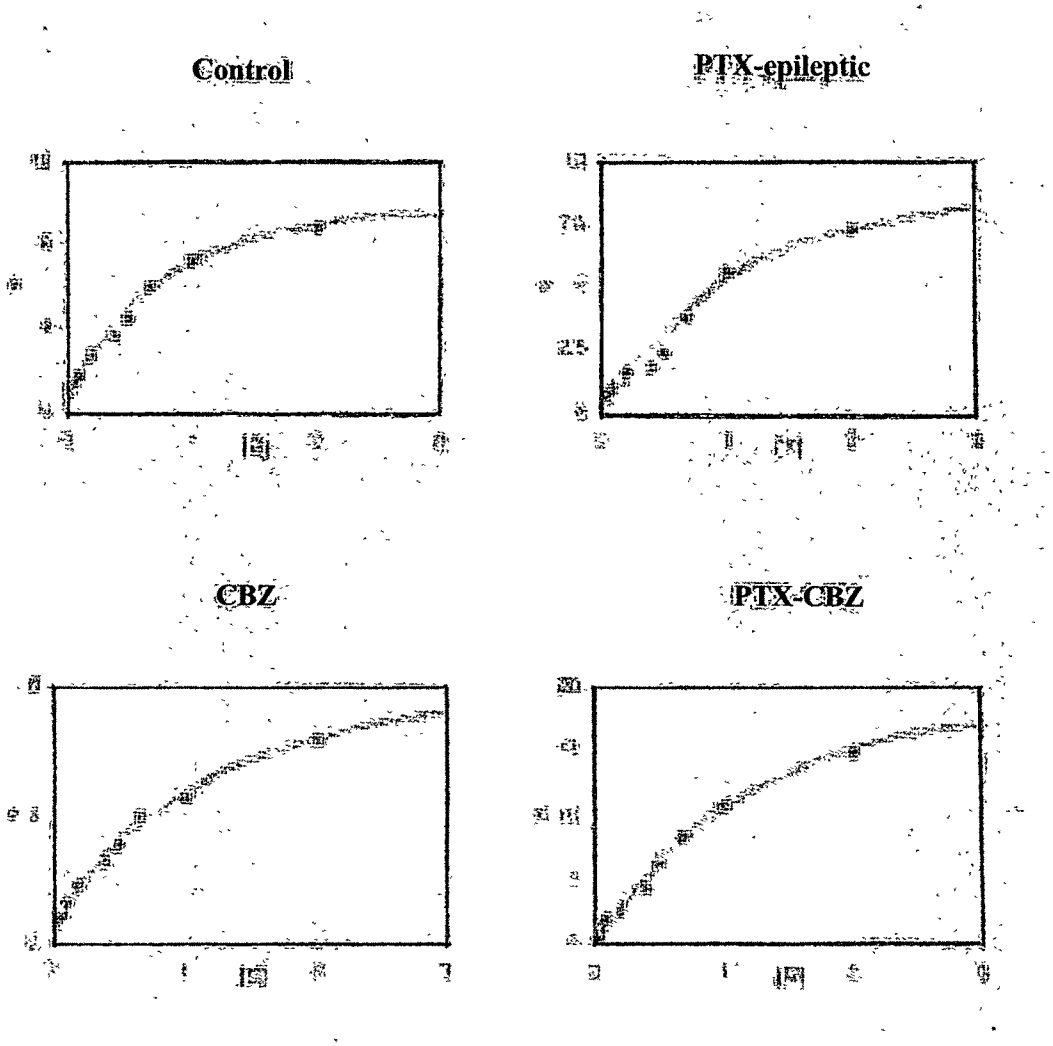


Figure 5. Typical substrate saturation curves for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with LTG and epileptic treated with LTG (PTX-LTG) animals. The experimental details are as given in the text. Concentration of ATP was in the range of 0.04-2 mM. The abscissa represents the reaction velocity v, while the ordinate represents [S]. Reaction velocity is in μmol Pi liberated/h/mg protein.

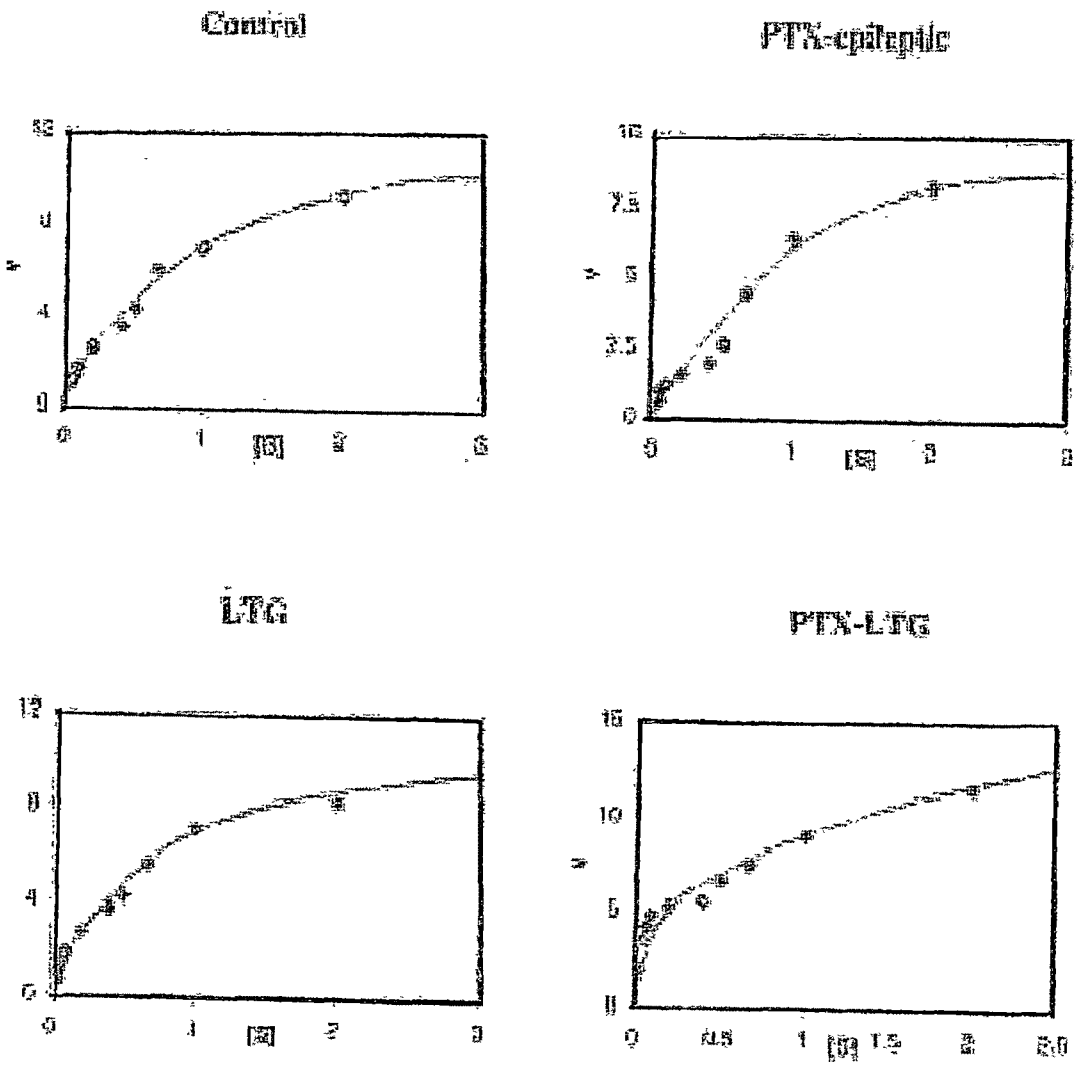


Figure 6. Typical substrate saturation curves for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with CLB and epileptic treated with CLB (PTX-CLB) animals. The experimental details are as given in the text. Concentration of ATP was in the range of 0.04-2 mM. The abscissa represents the reaction velocity *v*, while the ordinate represents [S]. Reaction velocity is in µmol Pi liberated/h/mg protein.

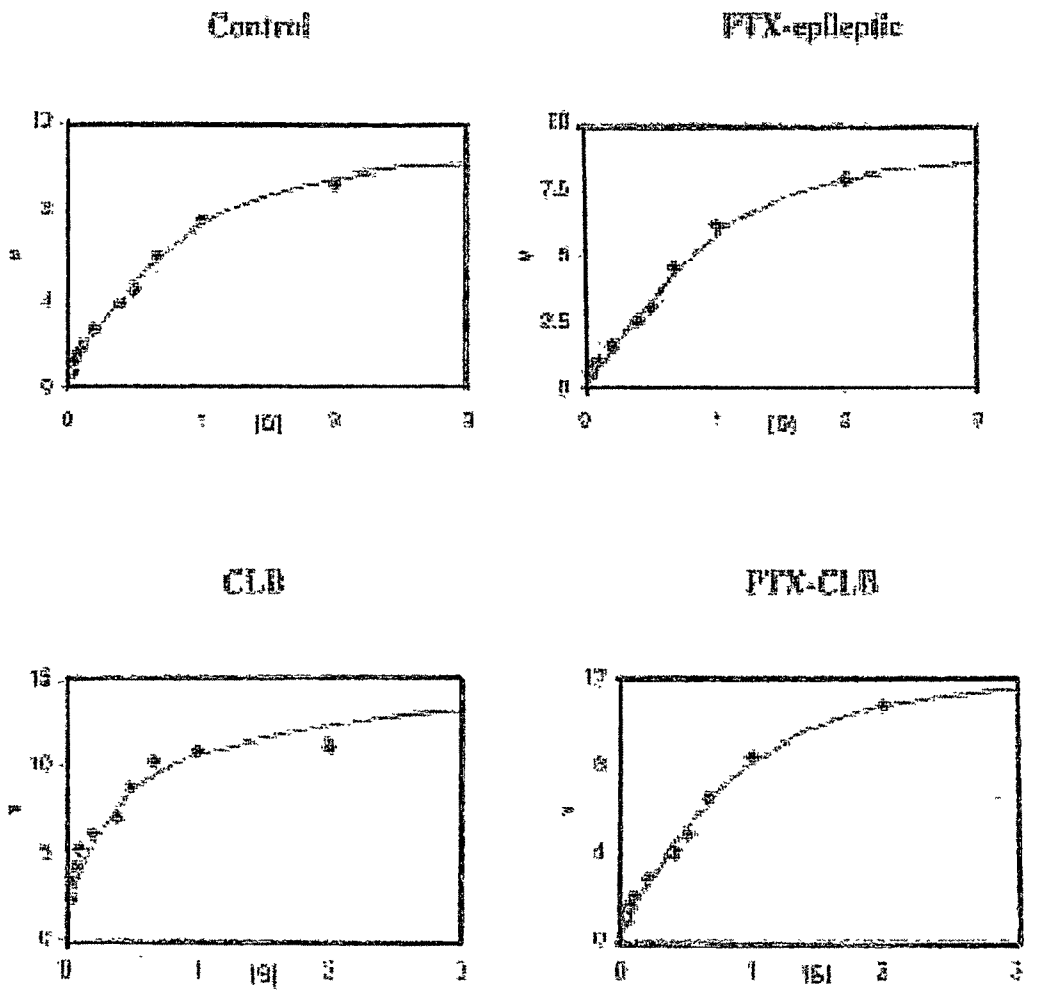


Figure 7. The respective Eadie-Hofstee plots for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with CBZ and epileptic treated with CBZ (PTX-CBZ) animals. The experimental details are as given in the text. Concentration of ATP was in the range of 0.04-2 mM. The abscissa represents the reaction velocity *v*, while the ordinate represents the *v*/[S] ratios. Reaction velocity is in µmol Pi liberated/h/mg protein. *v*/[S] is reaction velocity divided by the corresponding substrate concentration.

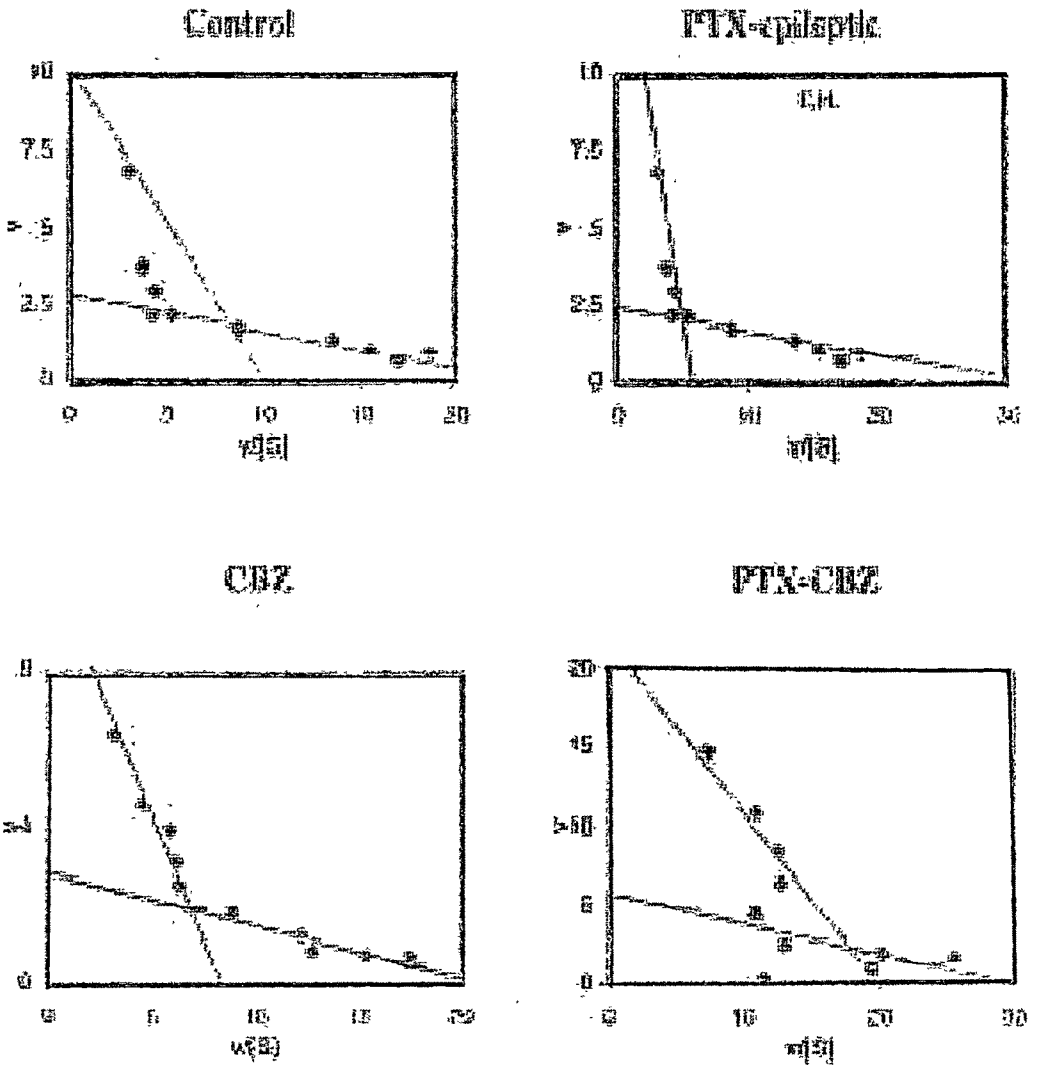


Figure 8. The respective Eadie-Hofstee plots for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with LTG and epileptic treated with LTG (PTX-LTG) animals. The experimental details are as given in the text. Concentration of ATP was in the range of 0.04-2 mM. The abscissa represents the reaction velocity *v*, while the ordinate represents the *v*/[S] ratios. Reaction velocity is in μmol Pi liberated/h/mg protein. *v*/[S] is reaction velocity divided by the corresponding substrate concentration.

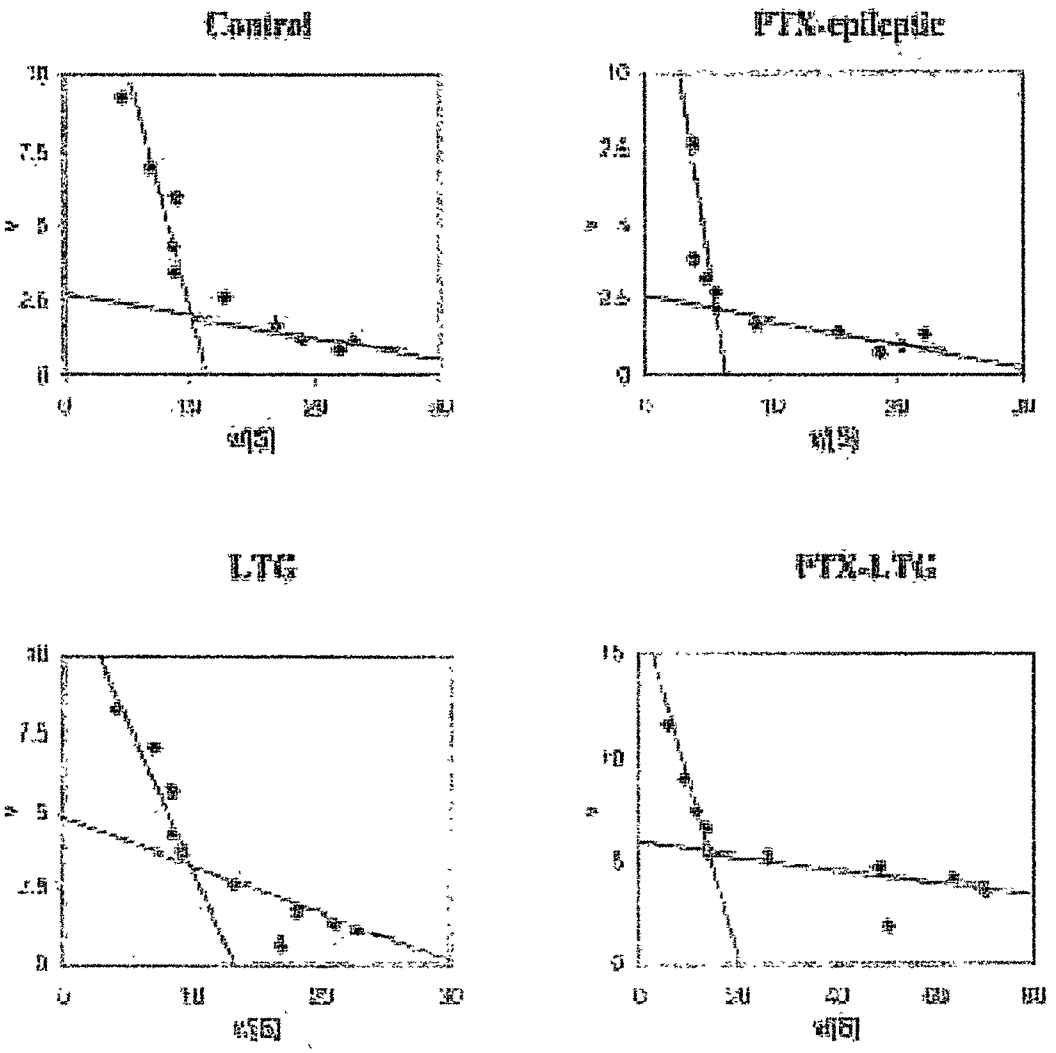


Figure 9. The respective Eadie-Hofstee plots for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with CLB and epileptic treated with CLB (PTX-CLB) animals. The experimental details are as given in the text. Concentration of ATP was in the range of 0.04-2 mM. The abscissa represents the reaction velocity *v*, while the ordinate represents the *v*/[S] ratios. Reaction velocity is in μmol Pi liberated/h/mg protein. *v*/[S] is reaction velocity divided by the corresponding substrate concentration.

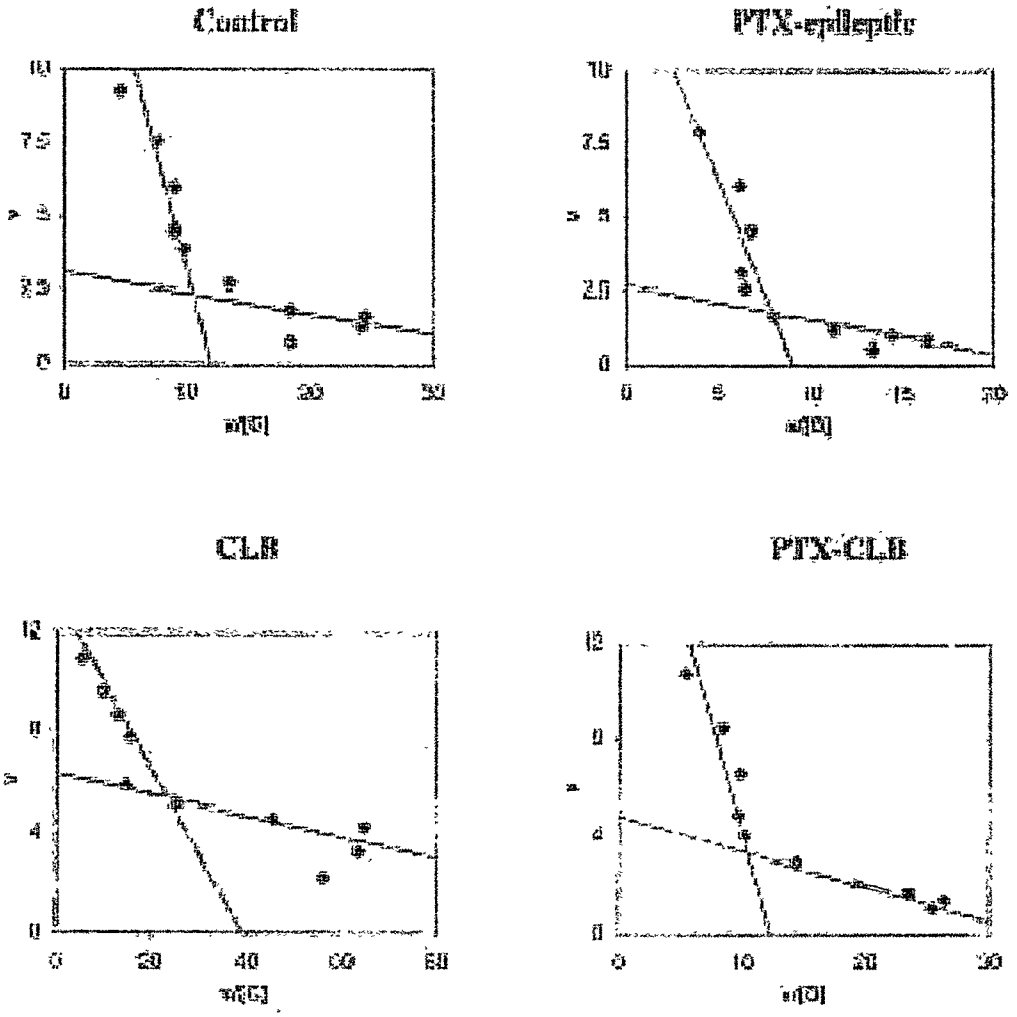


Table1: Effect of PTX-induced seizures on substrate kinetics of rat brain mitochondrial ATPase

Animals	Component I		Component II	
	K_m	V_m	K_m	V_m
Control (8)	0.14 ± 0.004	3.89 ± 0.097	1.20 ± 0.051	13.94 ± 0.51
PTX (8)	0.09 ± 0.003*	2.51 ± 0.061*	2.56 ± 0.221*	15.27 ± 0.37

Results are given as mean ± SEM of the number of observation indicated in the parentheses.
* $p<0.001$

Table 2: Effects of Carbamazepine (CBZ) treatment on temperature kinetics of rat brain mitochondrial ATPase in control and PTX-induced epileptic condition

Animals	Component I		Component II	
	K_m	V_m	K_m	V_m
Control	0.13 ± 0.007	3.50 ± 0.22	1.27 ± 0.07	13.11 ± 0.75
CBZ	0.17 ± 0.011*	3.21 ± 0.21	0.86 ± 0.02**	8.60 ± 0.36**
PTX	0.10 ± 0.007*	2.81 ± 0.20*	2.89 ± 0.25**	14.49 ± 0.79
PTX-CBZ	0.23 ± 0.009**, b	6.21 ± 0.32**, b	2.03 ± 0.15**, a	25.80 ± 0.73**, b

Results are given as mean ± SEM of 8 independent observations.
* $p<0.01$ and **, $p<0.001$ compared with Control.
a, $p<0.01$ and b, $p<0.001$ compared with PTX treated group.

Table 3: Effects of Lamotrigine (LTG) treatment on temperature kinetics of rat brain mitochondrial ATPase in control and PTX-induced epileptic condition

Animals	Component I		Component II	
	K_m	V_m	K_m	V_m
Control	0.14 ± 0.006	3.60 ± 0.21	1.16 ± 0.101	14.09 ± 1.01
LTG	0.19 ± 0.007**	5.40 ± 0.25**	0.87 ± 0.061*	11.72 ± 0.50*
PTX	0.11 ± 0.005**	2.97 ± 0.08*	2.69 ± 0.22**	12.69 ± 0.80
PTX-LTG	0.06 ± 0.033**, b	6.72 ± 0.28**, b	1.03 ± 0.062 b	15.52 ± 0.55 a

Results are given as mean ± SEM of 8 independent observations.
* $p<0.05$ and **, $p<0.001$ compared with Control.
a, $p<0.05$ and b, $p<0.001$ compared with PTX treated group.

Table 4: Effects of Clobazam (CLB) treatment on temperature kinetics of rat brain mitochondrial ATPase in control and PTX-induced epileptic condition

Animals	Component I		Component II	
	K_m	V_m	K_m	V_m
Control	0.12 ± 0.005	3.40 ± 0.16	1.57 ± 0.114	13.41 ± 0.48
CLB	0.13 ± 0.005	9.11 ± 0.22**	0.31 ± 0.023**	15.07 ± 0.57
PTX	0.10 ± 0.005**	2.77 ± 0.12*	2.71 ± 0.203**	14.15 ± 0.67
PTX-CLB	0.17 ± 0.006**, a	4.86 ± 0.21**, a	1.31 ± 0.071 b	13.83 ± 0.45

Results are given as mean ± SEM of 8 independent observations.
* $p<0.05$ and **, $p<0.001$ compared with Control.
a, $p<0.001$ compared with PTX treated group.

Treatment of epileptic animals with CBZ showed 1.6 to 2 fold increase in Km and Vm of both the components as compared to control (Table 2). To some extent, LTG treatment to the epileptic animals restored the Km and Vm to the control values (Table 3). CLB treatment showed similar pattern as CBZ treatment (Table 4). In general, all the three AEDs under study showed 1.7 to 1.9 times increase in Km and Vm for component I in the epileptic animals (Table 2-4).

In the light of altered substrate saturation kinetics (Table 1-4) it was of interest to find out the effect of PTX-induced convulsions and treatment with AEDs to control and epileptic animals on temperature dependent changes in the mitochondrial ATPase activity. The temperature kinetics data were analyzed in terms of Arrhenius plots to find out the energies of activation (E1 and E2) and phase transition temperature (Tt). The typical Arrhenius plots are shown in Fig 10-12. As can be noted, typical biphasic plots were obtained for control and treatment groups.

The data on energies of activation and phase transition temperature are given in Table 5 to 8. PTX-induced seizures resulted into 1.2 fold increase in both E1 and E2, while Tt was decreased by 4 °C (Table 5).

Figure 11. Typical Arrhenius plots for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with LTG and epileptic treated with LTG (PTX-LTG) animals. The experimental details are as given in the text. The ATPase activity was determined with 2 mM ATP. The abscissa represents reciprocal of absolute temperature $T \times 1000$. Reaction velocity is in μmol Pi liberated/h/mg protein and absolute temperature T in Kelvin.

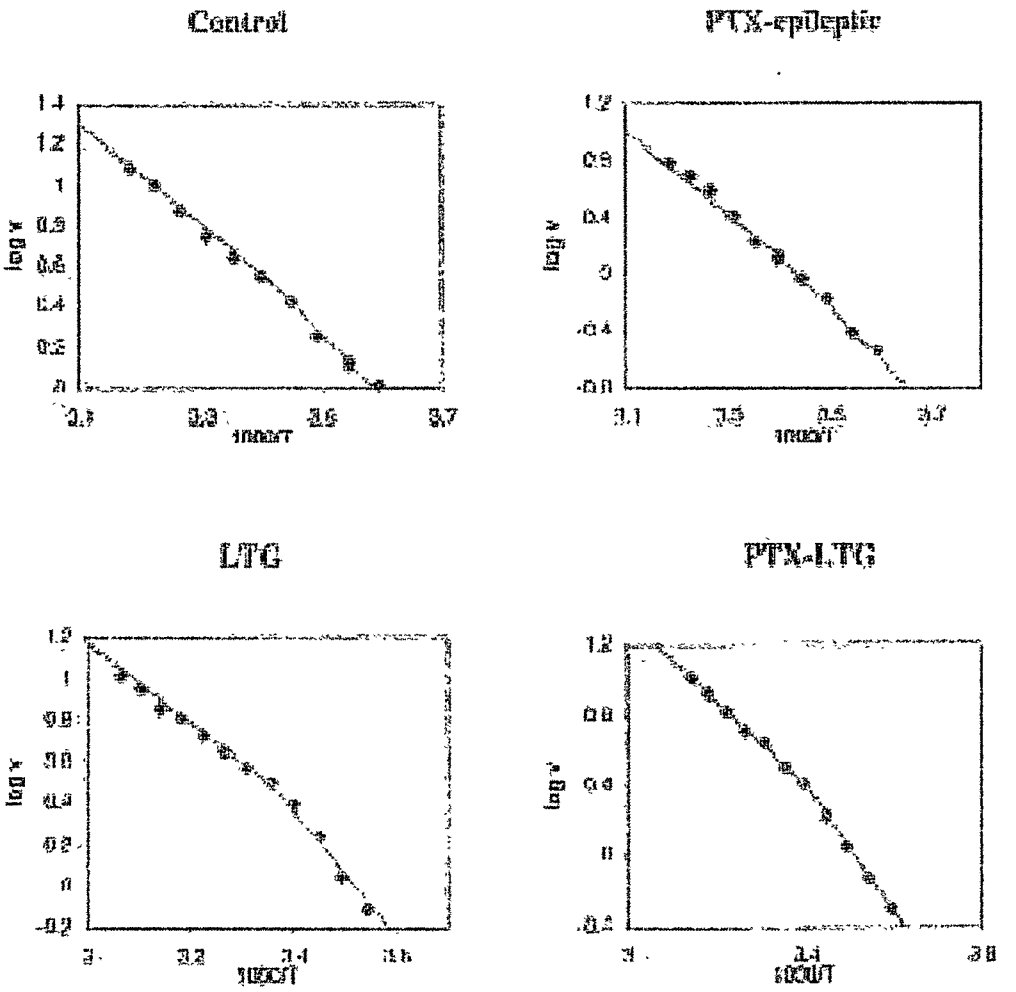


Figure 12. Typical Arrhenius plots for rat brain mitochondrial ATPase in control, PTX-epileptic, control treated with CLB and epileptic treated with CLB (PTX-CLB) animals. The experimental details are as given in the text. The ATPase activity was determined with 2 mM ATP. The abscissa represents reciprocal of absolute temperature $T \times 1000$. Reaction velocity is in μmol Pi liberated/h/mg protein and absolute temperature T in Kelvin.

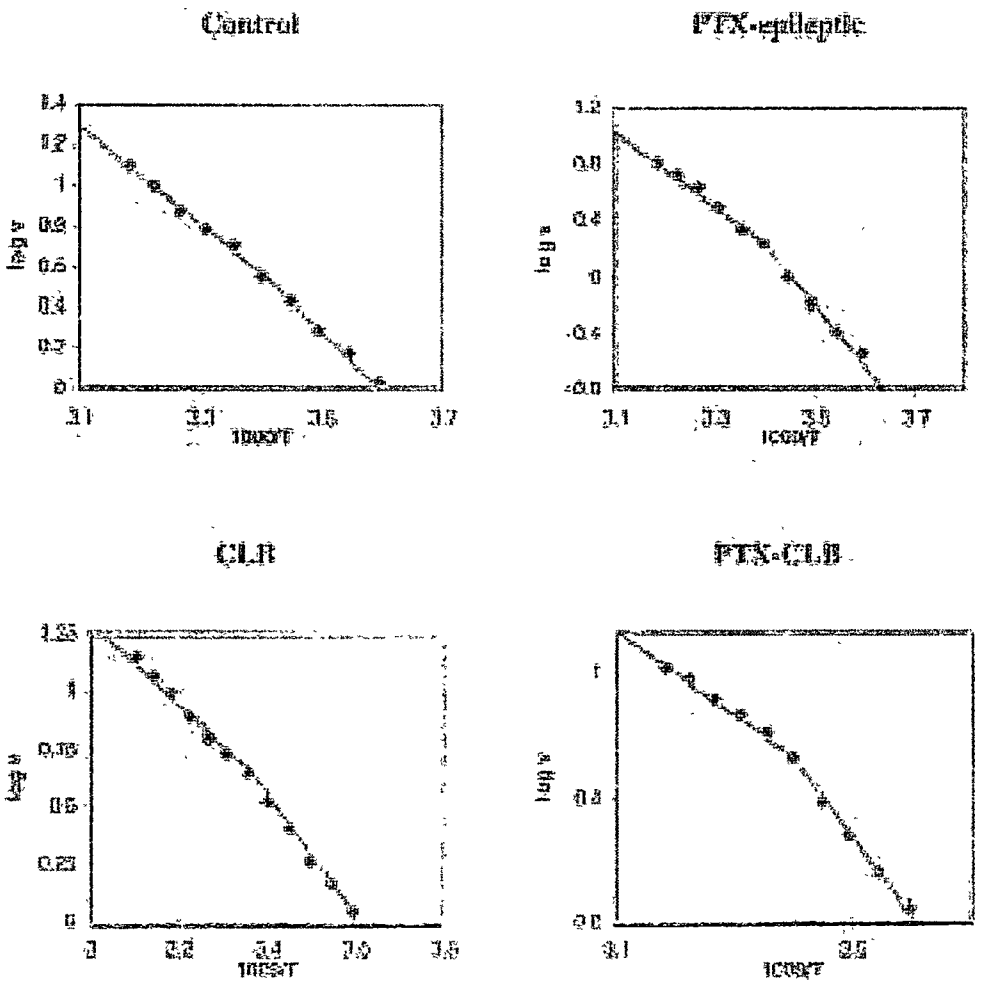


Table 5. Effect of PTX-induced seizures on temperature kinetics of rat brain mitochondrial ATPase

Animals	Energy of activation (KJ/mole)		Phase transition temperature (Tt °C)
	E1	E2	
Control (8)	42.04 ± 1.32	58.15 ± 1.46	23.67 ± 0.70
PTX (8)	49.16 ± 2.01*	64.84 ± 1.33*	19.75 ± 0.60**

Results are given as mean ± SEM of the number of observation indicated in the parentheses. *, $p<0.01$ and ** $p<0.001$

Table 6. Effects of Carbamazepine (CBZ) treatment on temperature kinetics of rat brain mitochondrial ATPase in control and PTX-induced epileptic condition

Animals	Energy of activation (KJ/mole)		Phase transition temperature (Tt °C)
	E1	E2	
Control (8)	42.04 ± 1.32	58.15 ± 1.46	23.67 ± 0.70
CBZ (8)	64.20 ± 1.11**	76.34 ± 1.06**	20.57 ± 0.28**
PTX (8)	47.95 ± 1.30*	62.64 ± 1.41*	18.92 ± 0.46**
PTX-CBZ (8)	42.45 ± 0.79 [a]	57.25 ± 1.47 [a]	24.73 ± 0.91[b]

Results are given as mean ± SEM of the number of observation indicated in the parentheses.

*, $p<0.05$ and ** $p<0.001$ compared with Control.

a, $p<0.05$ and b, $p<0.001$ compared with PTX treated group.

Table 7. Effects of Lamotrigine (LTG) treatment on temperature kinetics of rat brain mitochondrial ATPase in control and PTX-induced epileptic condition

Animals	Energy of activation (KJ/mole)		Phase transition temperature (Tt °C)
	E1	E2	
Control (8)	42.23 ± 1.41	57.10 ± 1.57	24.28 ± 0.77
LTG (8)	47.19 ± 1.27*	61.14 ± 1.35	27.88 ± 0.43**
PTX (8)	50.65 ± 1.93*	64.84 ± 1.33*	18.70 ± 0.55**
PTX-LTG (8)	38.07 ± 0.58*, b	52.61± 1.43 b	21.36 ± 0.81*, a

Results are given as mean ± SEM of the number of observation indicated in the parentheses.

*, $p<0.02$ and ** $p<0.001$ compared with Control.

a, $p<0.02$ and b, $p<0.001$.

Table 8. Effects of Clobazam (CLB) treatment on temperature kinetics of rat brain mitochondrial ATPase in control and PTX-induced epileptic condition

Animals	Energy of activation (KJ/mole)		Phase transition temperature (Tt °C)
	E1	E2	
Control (8)	43.42 ± 0.68	57.32 ± 2.06	22.62 ± 0.32
CLB (8)	49.43 ± 1.49*	53.12 ± 1.46	28.87 ± 0.57**
PTX (8)	49.30 ± 1.69**	63.76 ± 1.56*	18.81 ± 0.69**
PTX-CLB (8)	47.21 ± 0.97*	60.66 ± 1.39	17.57 ± 0.57**

Results are given as mean ± SEM of the number of observation indicated in the parentheses.

*, $p<0.05$ and ** $p<0.001$ compared with Control.

Treatment with AEDs to the control animals revealed 1.2 to 1.5 times increase in E1 with maximum extent was seen for CBZ treatment (Table 6-8, Fig 10-12). Tt was decreased by 3.3 °C after CBZ treatment while 4 to 6 °C elevation was observed in LTG and CLB treated groups. In general, differential effects of AEDs are evident on temperature kinetics.

CBZ treatment to epileptic animals resulted into the restoration of E1 and E2 and thus Tt back to the controls (Table 6, Fig 10). LTG treatment decreased E1 and E2 and thereby composite decrease in Tt (by 3 °C) was observed (Table 7, Fig 11). Treatment with CLB decreased E1 by 10% with 5 °C decrease in Tt in the epileptic animals (Table 9, Fig 12).

Uncoupling of mitochondrial respiratory chain activity lead to declined respiration, it could also affect the generation of the mitochondrial membrane potential that is linked to respiration by proton pumping i.e. F_oF_1ATPase. Significant alterations in ATPase activity and kinetic properties, which is observed here, could be an adaptation to the increased demand of energy during prolonged seizure activity. Decreased phosphate energy metabolism is suspected to play a particular role in seizure related neuronal damage (21, 22). Activity of the synaptic Mg^{2+}, Ca^{2+} dependent ecto-ATPase was also decreased in the epileptic condition (23). Increased excitability of neuronal membrane is reciprocated with decreased ATP levels in the cell and compromised mitochondrial ATPase (24, 25). The amount of ATP available to the neuron can therefore be considered as one of the key events in preserving neuronal integrity. In fact, there are many reports

that consider depleted ATP levels because of compromised mitochondrial ETC and ATPase is an indicator of loss of cell integrity / cytotoxicity / mitochondrial toxicity (26-30).

Reduced cytochrome c oxidase activity (31) – which is the terminal and rate limiting enzyme of the mitochondrial respiratory chain – can lead to incomplete reduction of oxygen, increased production of ROS and lower ATP synthesis by F_oF_1ATPase and thereby producing more oxidative damage to mitochondrial DNA and membranes (32-35). Possible mutations of mitochondrial DNA which is known to be extremely vulnerable due to the lack of protective histones and inadequate repair mechanisms (36) could lead to a decreased expression of the mitochondrial encoded subunits of the ETC. Additionally, generalized seizures have been observed in several forms of epilepsy which have been associated with mutations in mitochondrial tRNAs (37, 38). For example, mutations in polypeptide-coding mitochondrial genes have been reported in patients with epilepsy in the ATPase6 gene (37) that forms important component of proton channel in F_oF_1ATPase.

The differential effects of AEDs treatment to control and PTX-epileptic animals are noteworthy here. ATPase activity was restored to some extent after AED treatment to the epileptic animals. Whereas altered substrate and temperature kinetics properties was differentially altered and not restored by the AED treatment. In-fact AEDs exerted their own effect on the system, as evident from the AED treated control animals.

Antiepileptics are reported to be recognized as the modulator of mitochondrial function and neurotransmitter metabolism. *In vivo* and *in vitro* experiments with conventional AEDs like diazepam, valproate, phenytoin and phenobarbital showed that AEDs can directly or indirectly affect the mitochondrial respiration, oxygen utilization, respiratory chain enzyme activity and ATPase function in CNS (39-43).

Mitochondrial oxidative phosphorylation and ATPase function is the primary source of energy for cellular work. Thus, altered substrate and temperature kinetics following PTX-induced convulsions suggests that the system is trying to compensate for the decreased respiratory activity by changing the kinetic properties of ATPase.

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Summary

Complex V - F_oF_1ATPase - is the terminal component of mitochondrial ETC. The effect of PTX-induced epileptic condition and treatment with AEDs on mitochondrial ATPase kinetics properties were studied. PTX-induced seizures caused significant alterations in ATPase activity in the epileptic rat brain. Differential effects of AED treatment to control and the epileptic animals were observed, however treatment with AEDs to the epileptic animals reflects the restoration of ATPase activity to some extent. Altered substrate and temperature kinetics following PTX-induced seizures suggests that the system is trying to compensate for the decreased respiratory activity by changing the kinetic properties of ATPase. However, these alterations under the epileptic condition were not corrected by the treatment with AEDs; in fact AEDs exert their own effect on the system, as evident from the AED treated control animals.