

Anticonvulsant activity of gap-junctional blocker carbenoxolone in albino rats**Suneel Kumar Reddy¹, Navin A. Patil^{2*}, Vinod Nayak³, Smita Shenoy², Anoosha Bhandarkar⁴, Shankar M. Bakkannavar³, Rahul Kotian⁵**

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ABSTRACT

Background: Gap junctions (GJs) are clusters of channels that connect the interiors of adjoining neurons and mediate electrical/electrotonic coupling by transfer of ions and small molecules. Electrotonic coupling between principal neurons via GJs is increasingly recognized as one of the mechanisms in the pathogenesis of the abnormal neuronal synchrony that occurs during seizures. Carbenoxolone the succinyl ester of glycyrrhetic acid obtained from liquorice has been shown to have the property of blocking gap junctional intercellular communication. The objectives were to study if carbenoxolone has in-vivo anticonvulsive activity in pentylenetetrazole (PTZ) and maximal electroshock (MES) seizure models and to probe the functional role of GJs in seizures.

Methods: Carbenoxolone was tested for anticonvulsive effect in albino rats subjected to seizures by the PTZ and MES at three doses 100 m/kg, 200 m/kg, 300 m/kg. In the PTZ model parameters observed were seizure protection, seizure latency and seizure duration. In the MES model parameters observed were seizure protection and seizure duration.

Results: The results showed that the carbenoxolone has anticonvulsant activity in both PTZ and MES induced seizures with better protection in the PTZ induced seizures. In the PTZ model carbenoxolone produced a statistically significant increase in seizure latency, decrease in seizure duration and seizure protection. In the MES model carbenoxolone produced a statistically significant decrease in seizure duration.

Conclusions: Carbenoxolone has in-vivo anticonvulsive effect and could be useful in both petitmal (absence) seizures and grand mal (generalized tonic-clonic epilepsy) seizures. The protective effect of carbenoxolone could be due to blockade of GJ channels that mediate electro tonic coupling and thereby prevent the neural synchronization that is characteristic of seizures. The study also supports the view that GJs have a functional role in the electrophysiology of seizures and GJ blockers have potential as a new class of antiepileptic drugs.

Keywords: Carbenoxolone, Gap junctions, Anticonvulsant

INTRODUCTION

Epilepsy (the “sacred disease,” “falling sickness”) from 400 BC when Hippocrates described the sacred disease to

the modern 21st century sophistication continues to elude complete understanding. Despite the available therapeutic options, a significant number of patients continue to live with uncontrolled seizures/intractable epilepsy and/or

experience significant drug-induced adverse effects. The need, therefore, remains for the discovery of new drugs that are more efficacious therapies that do not impinge on the patients' quality of life.

In neural tissues intercellular communication also occurs by channels termed as gap junctions (GJs).¹ These GJs that are distinct from the synapses permit the transfer of small molecules and electrical ions between the adjoining neurons. This passage of electrical ions (chiefly K⁺) between the neurons couples the activity of the neurons to one and is called as electrotonic coupling. The gap junctional communication enables high-transmission speeds, the ability to transmit subthreshold signals in a reciprocal manner and synchronization of firing of neurons in a network.² Current evidence strongly suggests a role for gap junctional communication in neuronal synchrony and seizure generation under normal and pathological conditions.³

These insights that have been gained into the cellular and molecular mechanisms of epileptogenesis are being used in the development of newer antiepileptic drugs (AEDs) that act by interfering with those mechanisms-the mechanistic approach.

Evidence from in vitro studies shows that inhibitors of GJ communication can inhibit seizures discharges.⁴ The compound carbenoxolone, a derivative of glycyrrhetic acid, has been shown to have the property of inhibiting gap junctional interneuronal communication at the cellular level.⁵

The progression from discoveries of promising agents made at cellular and molecular levels into the next stage of development requires screening in validated animal models. Thus, carbenoxolone is being screened for anticonvulsive effects in vivo to validate the findings made at the cellular level into the mechanisms in epilepsy and also for possible development of a new class of AEDs.

With this background, the study aims to investigate the in vivo anticonvulsive effects of gap junctional blocker in the rodent model of seizures. The objectives are:

- To study if carbenoxolone has anticonvulsive activity in experimentally induced seizures in albino rats.
- To probe the functional role of GJs in seizures.

Review of literature

Epilepsy is a heterogeneous disorder, and a comprehensive clinical definition is difficult because of its varied manifestations. The cardinal feature of epilepsy is the occurrence of seizures.

A pathophysiologic definition initially proposed by Hughlings Jackson in 1873 still holds in which he defined the epilepsy as "an episodic disorder of the nervous system arising from synchronous and sustained discharge by a group of nerve cells".⁶

GJs

Bennett and Zukin have reviewed GJs and their role in the electrophysiology of the central nervous system (CNS).⁷ GJ is clusters of channels that connect the interiors of adjoining neurons and mediate electrical coupling and transfer of small molecules. The large internal diameter (1.2 nm) of many GJ channels allow the flow of electric current, largely carried by K⁺ ions and also exchange of small metabolites and intracellular signaling molecules (cyclic adenosine monophosphate [cAMP], IP3).

The connexons are hollow hexamers formed by the proteins connexins (Cxs). These Cx are the building blocks of the GJs (Figure 1).

There are 20 members of a gene family coding for the Cx. The various Cx are named by numbers representing their molecular mass in kDa. Table 1 shows the different types of Cx expressed in the mammalian CNS with their differing cell specificity.

GJs and seizures

Hypersynchronicity between adjacent neurons in a neuronal population is an important feature of the discharge in a seizure. Since GJ mediate synchronization by electrotonic coupling in the neurons, it began to be considered that a non-synaptic mechanism via GJs may have a role in the abnormal hypersynchrony seen in epileptogenesis.^{8,9}

Experimental manipulation of the GJ activity using GJ blockers and enhancers of GJ communication also suggested that GJ could perhaps have a role in seizures mediating the hypersynchronicity.¹⁰⁻¹²

Carbenoxolone

Carbenoxolone is a synthetic triterpenoid derived from glycyrrhizic acid a natural constituent of liquorice. Liquorice is a sweetening and flavoring agent obtained from *Glycyrrhiza glabra*.

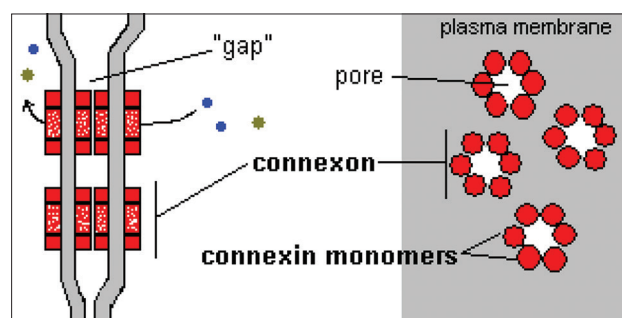


Figure 1: Gap junctions (Grey shade- neuron; Red shade – connexons monomers forming the gap junction channel; blue dots – small molecules; yellow dots-ions).

Carbenoxolone sodium is white or pale colored hygroscopic powder that is freely soluble in water, sparingly soluble in alcohol. It was formerly used as an ulcer healing agent in gastric ulcer. It helped by augmentation of mucous production, prolongation of lifespan of gastric epithelial cells, prevention of bile reflex and slow degradation of gastric mucus.¹³ It inhibits the enzyme 11- β -hydroxysteroid dehydrogenase, which is responsible for it having a mineralocorticoid like property causing Na⁺ and water retention and K⁺ loss.¹⁴ It also inhibits the intercellular GJs.⁵ Because of this property it is being investigated for potential anticonvulsant properties by blocking GJ mediated hypersynchronicity in seizures.

METHODS

Experimental animals

The experiment was conducted on healthy male Wistar albino rats weighing between 150 and 200 g showing normal behavior and activity. The rats were previously unused for any other experiment. These animals, housed under standard conditions with free access to food and water, were obtained from the Central Animal House, JJM Medical College, Davangere (India). The study was conducted with the approval of the Institutional Ethical Committee, JJM, Medical College, Davangere, India and in accordance with their guidelines.

Drugs and chemicals

Pentylentetrazole (PTZ) and carbenoxolone manufactured by Sigma, USA and diazepam manufactured by Ranbaxy, India were procured through Nice Chemicals, Bangalore. Normal saline was prepared in the Pharmacy Laboratory, JJM Medical College, Davangere. All drugs to be administered to the rats were dissolved in normal saline.

Methodology

Carbenoxolone was tested for anticonvulsant in two in-vivo models of experimentally induced seizures.

- PTZ induced seizures – chemoconvulsions
- Maximal electroshock (MES) induced seizures.

PTZ method

For this model the rats were arranged in 5 groups of 7 rats each as follows:

- PC: control group (normal saline)
- PS: standard drug (diazepam) group - 0.5 mg/kg
- P1: test drug (carbenoxolone) group - 100 mg/kg
- P2: test drug (carbenoxolone) group - 200 mg/kg
- P3: test drug (carbenoxolone) group - 300 mg/kg.

The grouped rats were marked for identification and placed in separate labeled cages. The test drug, standard drug and PTZ were dissolved in normal saline for administration. The drugs were injected to rats prior to subjecting them to chemoconvulsion by PTZ (70 mg/kg s.c. into the scruff of the neck). The control group rats were injected normal saline i.p. 60 min before, the standard group were injected diazepam i.p. 30 min before and test groups were injected carbenoxolone i.p. 60 min before. Animals are observed over a 30 min for the occurrence of seizures.

The occurrence of tonic clonus for more than 5 s was taken as a positive seizure response and abolition of tonic clonus was considered as protection against PTZ seizures. The parameters noted were:

1. Occurrence of seizure
2. Seizure latency (time for onset of seizure)
3. Duration of tonic clonus.

MES method

The rats being experimented in this model were arranged into 5 groups of 7 rats each as follows:

- MC: control group (normal saline)
- MS: standard drug (diazepam) group - 5 mg/kg
- M1: test drug (carbenoxolone) group - 100 mg/kg
- M2: test drug (carbenoxolone) group - 200 mg/kg
- M3: test drug (carbenoxolone) group - 300 mg/kg

The grouped rats were marked for identification and placed in separate labeled cages. The test and standard drugs were dissolved in normal saline for administration. The rats were injected the drugs prior to subjecting them to electroshock. The control group rats were injected normal saline i.p. 60 min before the electroshock, the standard group were injected diazepam i.p. 30 min before and test groups were injected carbenoxolone i.p. 60 min before.

The electroconvulsimeter was set to deliver a current of 150 mA for 0.2 s. The 2 earclip electrodes of the electroconvulsimeter were applied one to each ear after moistening the ears. The rats were then stimulated transauricularly and observed. The occurrence of a tonic hindlimb extensor was taken as a positive response for MES. Abolition of tonic hindlimb extensor was taken as protective against MES seizures. The following parameters were noted.

1. Occurrence of seizure (tonic hindlimb extension)
2. Duration of seizure.

RESULTS

The results of the study in MES and PTZ seizure models showing comparison between groups are depicted in Tables 2 and 3.

The data recorded in each of the groups were expressed as mean±standard error for that group. The test groups were compared with the control and the Tukey-Kramer was used to compare for levels of significance.

PTZ model

In the PTZ model carbenoxolone increased the latency of seizures, decreased the duration of seizures and protected against the development of seizures.

Table 1: Cxs expressed in cells of the mammalian central nervous system.⁷

Cell type	Cx
Neocortex	
P1-P14, adult CA3, cerebellum	Cx45
Inferior olive	Cx36
Mitral cells, olfactory bulb	Cx36, Cx43, Cx45
Motoneurons	Cx36, Cx43, Cx47
Locus coeruleus	Cx43
Retina	
Rods, cones, AII amacrine cells	Cx36
Horizontal cells	Cx57
Glial cells	
Astrocytes	Cx43, Cx26, Cx30
Oligodendrocytes	Cx32, Cx29, Cx47
Microglia	Cx43, Cx36

Cx: Connexin

Latency

A dose-dependent increase in the mean latency of seizure onset was seen as depicted in the Figure 2. At a dose of 100 mg/kg the mean time of onset of seizures (latency) was higher in the test groups (carbenoxolone) compared to control group (normal saline) but this was not statistically significant (p>0.05). The greater mean latency of seizures observed at a dose of 200 mg/kg of carbenoxolone was statistically significant (p<0.05) compared to the control and at a dose of 300 mg/kg of carbenoxolone it was statistically highly significant (p<0.001) compared to the control.

Duration of seizures

Carbenoxolone produced a dose dependant decrease in the mean of duration seizures in the test animals as depicted in

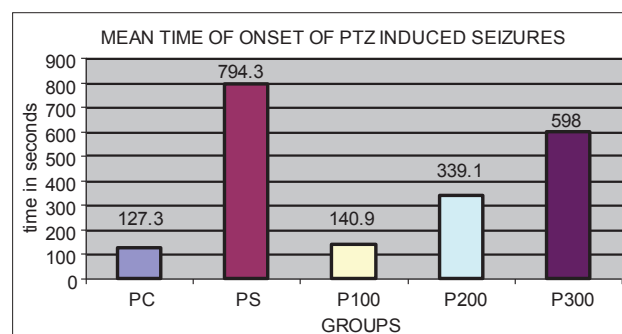


Figure 2: PC: normal saline, PC: diazepam 0.5 mg/kg, P100:carbenoxolone 100 mg/kg, P200: carbenoxolone 200 mg/kg, P300: carbenoxolone 300 mg/kg.

Table 2: Comparison between groups with PTZ induced seizures.

Rat group	Mean seizure latency (mean±SE)	p value	Mean seizure duration (mean±SE)	p value	Seizure protection %
PC	127.3±5.97	-	767±15.76	-	0
PS	794.3±50.65 ***	<0.0001	80.3±38.17***	<0.0001	57.14
P100	140.9±3.7^	0.078	719.7±17.65^	0.069	0
P200	339.1±93.73*	0.044	463.1±80.13*	0.0029	14.28
P300	598±107.34***	0.0009	298.9±77.48***	<0.0001	28.56

PC: Normal saline, PC: Diazepam 0.5 mg/kg, P100: Carbenoxolone 100 mg/Kg, P200: Carbenoxolone 200 mg/Kg, P300: Carbenoxolone 300 mg/Kg. Results are expressed as mean±SE and analyzed for significance by the Tukey-Kramer test. ^p>0.05 not significant, *p<0.05 significant, **p<0.01 very significant, ***p<0.001 highly significant. SE: Standard error, PTZ: Pentylenetetrazole

Table 3: Comparison of groups with MES induced seizures.

Rat group	Drug	Seizure %	Seizure duration (mean±SE)	p value	Seizure protection %
MC	Normal saline	100	10.6±0.57	-	0
MS	Diazepam	42.85	3.1±1.52***	0.0006	57.14
M100	Carbenoxolone 100 mg/Kg	100	9.7±0.71^	0.37	0
M200	Carbenoxolone 200 mg/Kg	100	9.1±0.51^	0.086	0
M300	Carbenoxolone 300 mg/Kg	100	8.6±0.48*	0.02	0

Results are expressed as mean±SE and analyzed for significance by the Tukey-Kramer test. *p<0.05 significant, ***p<0.001 highly significant, ^p>0.05 not significant. SE: Standard error, MES: Maximal electroshock

Figure 3. The mean duration of seizures was lesser in the test groups than the control at all the three doses tested. At a dose of 100 mg/kg of carbenoxolone this was not statistically significant ($p>0.05$) compared to control. At a dose of 200 mg/kg of carbenoxolone the lesser mean duration of seizures was statistically significant ($p<0.05$) compared with the control and at a dose of 300 mg/kg of carbenoxolone it was statistically highly significant ($p<0.001$) compared with control.

Seizure protection

Carbenoxolone produced a 14.24% and 28.56% protection against the development of seizures at doses of 200 mg/kg and 300 mg/kg respectively. However, this was less than the protection afforded by the standard drug (diazepam) that produced 57.14% protection.

MES model

In the MES model carbenoxolone decreased the duration of seizures but did not afford any protection against the occurrence of seizures.

Duration of seizures

Carbenoxolone produced a dose dependant decrease in the mean of duration seizures in the test animals as depicted in Figure 4. The mean duration of seizures was lesser in the test groups than the control group at all the three doses tested. The lesser mean duration of seizures by carbenoxolone at a dose of 100 mg/kg and 200 mg/kg was not statistically significant ($p>0.05$) compared to control. At a dose of 300 mg/kg of carbenoxolone the lesser mean duration of seizures was statistically significant ($p<0.05$) compared to control.

Seizure protection

Carbenoxolone did not afford any protection against the occurrence of seizures at all the three tested doses. The standard control gave a protection of 58.14% against the development of seizures.

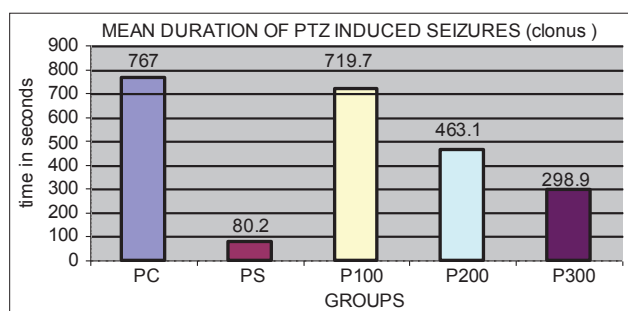


Figure 3: PC: diazepam 0.5 mg/kg, PS: normal saline, P100: carbenoxolone 100 mg/kg, P200: carbenoxolone 200 mg/kg, P300: carbenoxolone 300 mg/kg.

DISCUSSION

Although there are a large number of models that could potentially be used to screen for anticonvulsant activity, the MES model and the subcutaneous PTZ model remain the “gold standards” in early stages of testing.¹⁵ The results of the study conducted demonstrate that carbenoxolone has anticonvulsant activities in both PTZ and MES seizure models.

In this study the protection provided by carbenoxolone seems to be stronger in the PTZ model than the MES model. In the PTZ model carbenoxolone provides seizure protection (prevents the occurrence of seizures) in addition to reducing the duration of seizures. In the MES model carbenoxolone only produced a reduction in the seizure duration but did not provide seizure protection.

The results of this study support similar studies conducted on mice by Hosseinzadeh et al in which carbenoxolone showed anti convulsant activity in both PTZ and MES models.¹⁶ A study by Ambawade et al. on an ethanolic extract of *G. glabra* showed activity against the PTZ modeled seizures but not in the MES model. The extract of *G. glabra* contains derivatives of glycyrrhizinic acid of which carbenoxolone is a semi-synthetic derivative.¹⁷ Drugs that are effective in the PTZ model are usually thought to have activity against absence seizures (petit-mal seizures) and drugs showing activity in the MES model are presumed to have effect against tonic-clonic seizures (grand mal seizures).¹⁸

Role of GJs and blocking agents in seizures

Electrotonic coupling through the GJs, electrical field effects mediated via the extracellular space and the alteration of extracellular and intracellular ions during neural activity have been considered to play hypothetical roles in the synchronization of epileptiform activity (prolonged and hypersynchronous burst discharges).² These mechanisms are often considered “non-synaptic” because they are independent of active chemical synaptic transmission.

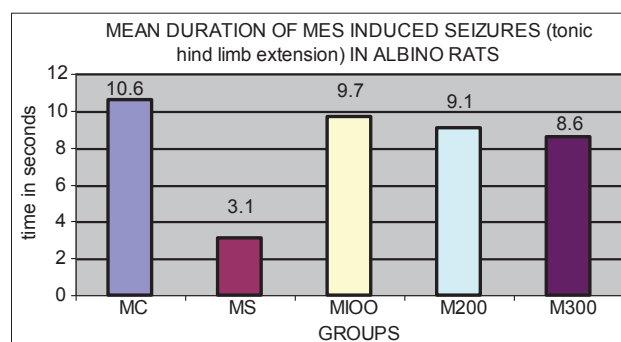


Figure 4: MC: Control group, MS: standard group (diazepam), M100: test group (carbenoxolone 100 mg/kg), M200: test group (carbenoxolone 200 mg/kg), M300: test group (carbenoxolone 300 mg/kg).

The role of GJs came into focus after several studies demonstrated that it was possible for seizure like activity to be initiated in hippocampal slices even in the absence of active chemical synaptic transmission by neurotransmitters.^{19,20} Since then the possible role of GJs in neural synchrony and in the pathological state of seizures have been the focus of considerable research, the idea being they could be the targets for developing of an entirely novel class of antiseizure drugs.

Electrophysiological, pharmacological, molecular biologic and computer modeling studies seem to indicate that they could be a participant in the characteristic hypersynchrony of seizures.

In vitro and in vivo pharmacological manipulation of GJs by using inhibitors of gap junctional communication and promoters of gap junctional communication also suggest a role in seizures. Blockers of GJs showed a reduction of the duration and amplitude of seizure discharges whereas opening of the GJs with trimethylamine (an intracellular alkalinizing agent that opens GJ channels) increased the duration and amplitude of the seizure discharges.²¹

In human neocortical slices obtained from temporal lobe epilepsy patients, intracellular and field potential recordings after the application of 4-aminopyridine showed that GJ played a role in the synchronizing human neocortical neural networks.²² In these tissues the synchronicity of spontaneous epileptiform activity was seen to be decreased within 20 min of application of GJ blockers (carbenoxolone, octanol, quinine, quinidine) with complete desynchronization seen at higher doses and longer times of application.

The expression of the neural specific component of the GJs at the epileptic foci was observed to be enhanced in induced seizures.²¹ The levels of the connexons Cx32, Cx43, Cx36 messenger RNAs (mRNAs) that code for components of the GJs were increased implying GJs are increased in response to a seizure.

The electrotonic coupling occurring through the GJs are not expected to be solely responsible for seizure activity because seizure activity also requires a mechanism for excitation (action potential, EPSP). The GJs are in fact considered to mediate the hyper synchronicity of firing of the neural tissue networks at the seizure locus rather than the hyperactivity.

In the electroencephalogram of the brain a short-term synchronization of neuronal electrical activity is reflected in characteristic periodic high frequency oscillations (>100 Hz). It has been seen that in the epileptic brain high frequency spontaneous oscillations in the range of 250-600 Hz occur and reflect the action potential bursts of synchronously discharging neuronal clusters. It is suggested that GJs may account for these high frequency bursts characteristic of seizures.^{8,23}

Early electrophysiological evidence suggested that only a few percent of the interneurons exhibit electrical coupling. However, subsequently studies have shown that it is possible for synchronization to occur in spite of a low coupling coefficient and when electrotonic coupling is combined with the recurrent excitatory synapses, these could act synergistically producing a hyper synchronous condition.²

Mechanism of action of carbenoxolone

The exact mechanism of action of carbenoxolone is still speculative. Carbenoxolone is supposed to bind to the Cx molecules of the GJs between neurons, leading to a conformational change and this possibly leads to closure of the GJs.²⁴ This blockade could hinder the development of electrotonic coupling between neural populations and thereby prevent neuronal synchronization in the brain. Synchronization being an important feature in the electrophysiology of seizure spread, the blockade could be the reason for the anti-seizure activity of carbenoxolone.

Another action of carbenoxolone could be preventing the increased expression of the Cx gene which codes for Cx proteins that are the structural components of the GJs. This is because animals treated with carbenoxolone have shown reduced levels of Cx mRNAs.²⁵ However, this is unlikely in this study in considering the time duration necessary.

CONCLUSION

Carbenoxolone has in vivo anticonvulsant activity in both PTZ and MES induced seizures and may be useful in absence seizures and tonic-clonic seizures.

- The anticonvulsant action is better against PTZ induced seizures than MES seizures
- The study lends support to the view that GJs have a role in pathophysiology of seizures
- Pharmacological agents that block GJs blockers could represent a potential new treatment for epilepsy.

Carbenoxolone, a semi-synthetic derivative of liquorice has been shown to have the property of blocking gap junctional channel communication between neurons. Gap junctional communication is distinct from classical synaptic neurotransmission. GJs are channels between neurons that allow almost instant transmission of impulses among neurons. This happens by the phenomenon of electrical/electrotonic coupling that is mediated by ions and transfer of small molecules. This helps in synchronizing firing among neuronal networks and may also have a role in the hypersynchronicity that is characteristic of epileptiform discharges. This study investigates the anticonvulsive affect of a gap junctional carbenoxolone and thereby the role of GJs in seizures.

Two well-established preliminary screening models of seizures were chosen to evaluate the anticonvulsive effect

of carbenoxolone - PTZ and MES induced seizures in albino rats. The ability of carbenoxolone to protect against the development of seizures and on the seizure latency and the seizure duration in the albino rats subjected to PTZ and MES were observed.

The results of the study indicated that carbenoxolone has an anticonvulsive effect in both PTZ and MES modeled seizures. Drugs effective in the PTZ model usually to have a protective effect in petit mal (absence) seizures and drugs effective in MES model in grand mal (generalized tonic-clonic) seizures.

The anticonvulsant activity could be due to the binding of carbenoxolone to the connexons that forms the channels of the GJs and inducing a conformational change. This prevents gap junctional communication between neurons and hinders the development of the synchronization necessary for seizure activity.

The study also provides evidence for the possible role of GJs in seizure as blocking of the GJs was associated with a protective effect against seizures. GJs could therefore be promising targets in the search for new AEDs.

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Ethical approval: The study was approved by the Institutional Animal Ethics Committee

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