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The Potential Role of ATP-sensitive Potassium Channels in Treating Epileptic Disorders

Chin-Wei Huang

*Department of Neurology, National Cheng Kung University, Tainan
Taiwan*

1. Introduction

Despite antiepileptic drug (AED) therapy, epilepsy remains uncontrolled in around one third of patients. The majority of current AEDs fall into two pharmacological classes, those that modulate neuronal voltage-gated sodium and calcium channels and those that modulate neurotransmitters. There is a need for new AEDs with novel mechanisms of action to serve as adjunct therapy for the treatment of intractable epilepsy. Among the diverse molecular targets, to selectively modify the excitability of neurons so that high frequency epileptic firing can be blocked without disturbing normal neuronal activity, potassium is a potential target. Potassium channels play a major role in the control of resting membrane potential, responsiveness to synaptic inputs, spike frequency adaptation and neurotransmitter release. Among them, the important metabolic coupler to electrical activity- ATP-sensitive potassium (K_{ATP}) channels provides a distinct link between the metabolic and electrical state of cells. We have demonstrated the role of K_{ATP} channels in epileptic seizures in diabetic hyperglycemia, providing the direct evidence that increases in extracellular glucose and intracellular ATP attenuate K_{ATP} channels, leading to a more excitable state. We also examined the K_{ATP} channel agonist mediating neuroprotection in diabetic individuals with status epilepticus. Here, we report how we investigated the diabetic hyperglycemia-related epileptic disorder from clinical observation to experimental studies, and review this potential novel mechanism underlying attenuating epileptic activities by opening K_{ATP} channels, especially related to metabolic syndrome.

2. Epileptic seizures in diabetic hyperglycemia: From clinical observation

More than 200 million persons worldwide will be diagnosed with diabetes (Mandrup-Poulsen, 1998). Epileptic seizures with diabetic hyperglycemia (DH) (Maccario et al., 1965; Venna and Sabin, 1981; Huang et al., 2005) are not uncommon and around one-fourth of DH patients have reported seizures (Venna and Sabin, 1981; Singh and Strobos, 1989). In more than half of these patients, seizures reveal previously undiagnosed diabetes (Venna and Sabin, 1981; Tiamkao et al., 2003; Harden et al., 1991).

Most seizures in DH are partial motor seizures (Singh and Strobos, 1989; Loeb, 1974; Tiamkao et al., 2003), while 15% present as status epilepticus (SE). The level of hyperosmolarity and hyponatremia, accompanied by a wide range of hyperglycemic symptoms, however, are inconsistent (Grant and Warlow, 1985). Previous case reports

suggest that DH-related epileptic seizures often develop at higher levels of glucose than non-DH-related seizures (Maccario et al., 1965; Venna and Sabin, 1981; Harden et al., 1991). We conducted a prospective comparative follow-up study, focusing on newly diagnosed unprovoked seizures in adult patients, with and without DH, from 2000 to 2004 (Huang et al., 2008). We found that seizure clustering in initial presentation and in recurrence in the DH group was significantly higher than that in the non-DH group. Patients with poor glycemic control (HbA1c >9%) had significantly higher risk of seizure recurrence and clustering. Thus, DH might play a role in the severity of newly diagnosed adult epileptic seizures. Severe seizures might beget seizures in these patients. DH should be intensively investigated in adult patients with newly diagnosed seizures and aggressive blood sugar control might benefit seizure treatment in these patients, more than AEDs would.

The pathophysiology of epileptic seizures in DH is probably multi-factorial. Glucose itself could enhance synaptic transmission and propagation, leading to more excitable neurons (Tutka et al., 1998; Gispen and Biessels, 2000) and even epileptic seizures (Schwechter et al., 2003), regardless of the presence of organic lesions. Underlying focal ischemia has also been suggested as having a role in triggering these partial seizures (Singh and Strobos, 1989). Seizure susceptibility even in only moderate degrees of hyperglycemia has been reported in previous studies (Tiamkao et al., 2003; Brick et al., 1989); our study suggests that glucose itself is a pro-convulsant in DH.

In clinical observation, in the DH group, patients with recurrent seizures had more frequent SE at initial seizure presentation than those without, suggesting potential kindling during poorly controlled DH. In poorly controlled diabetes, neither the continued use of AEDs nor the presence of organic structural lesions affects seizure recurrence. Although simple partial seizures are more common in DH-related epileptic seizures, complex partial seizures, as the second most common in this study, and some rarer presentations, such as reflex, parieto-occipital, and sensory seizures (Brick et al., 1989; Huang et al., 2005, 2006, 2010; Lavin, 2005), should be carefully evaluated.

In animal experiments, a higher glucose level have facilitated amygdaloid kindling in rats (Priel et al., 1991) and decreased the time required for 50% of rats to recover sufficiently from a first maximal electroshock seizure (MES) to be able to have another MES (White et al., 1986). This is compatible with seizure clustering in the DH group observed in this study. This further suggests that kindling may continue and seizures may recur if blood glucose remains high.

Failure to identify the possible association between DH and seizures is common in clinical practice, potentially leading to inadequate treatment and seizure recurrences. Early recognition of the link will help early diagnosis and treatment, and prevent unnecessary interventions.

3. Epileptic seizures in experimental animals with diabetic hyperglycemia

As we all know, glucose plays a major role in metabolism and cerebral functions. However, the effects of hyperglycemia on the central nervous system (CNS) and neuronal excitability (Biessel et al., 1994; Stewart et al., 1999; Gispen and Biessel, 2000) are not fully understood. High glucose concentrations have been associated with a lower seizure threshold in an animal model with a single seizure (Schwechter et al., 2003) and neuronal excitability and seizures are related to rapid glucose utilization and glycolysis (Greene et al., 2003). Experimentally, the correlation between extracellular glucose concentration and excitability

(seizure) has been established in previous studies (Margineanu et al., 1998; Tutka et al., 1998; Schwechter et al., 2003).

In addition to increasing excitability, higher glycosylated hemoglobin values have been associated with moderate declines in motor speed and psychomotor efficiency (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study Research Group et al., 2007). In animal models of diabetes, spatial-learning impairments occur in association with distinct changes in hippocampal synaptic plasticity (Biessels et al., 1998; Kamal et al., 2000). On the other hand, cognitive impairments after SE have been reported in both clinical and experimental studies (Helmstaedter, 2007). Nevertheless, how synaptic plasticity change responds to SE in DH is currently unknown. In addition, it remains to be determined whether DH exaggerates the cognitive and pathological outcome of SE.

We examined whether SE in rats with DH caused acute neuronal damage in the hippocampus, and impaired learning and memory, and synaptic plasticity, to determine the behavioral, pathological, and electrophysiological effects of SE on diabetic animals. Adult male Sprague-Dawley rats (150-200 g) were first divided into groups with and without streptozotocin (STZ)-induced diabetes, and then into treatment groups given a normal saline (NS) (STZ-only and NS-only) or a lithium-pilocarpine injection to induce SE (STZ+SE and NS+SE). Serial Morris water-maze test and hippocampal pathology results were examined before and 24 hours after SE. We found the STZ+SE group had a significantly higher percentage of severe seizures and SE-related death and worse learning and memory performances than the other three groups. The STZ+SE group, followed by the NS+SE group, showed the most severe neuronal loss and mossy fiber sprouting in the hippocampal CA3 area.

Tetanic stimulation-induced long-term potentiation (LTP) in a hippocampal slice from these rats was recorded in a multi-electrode dish system (Huang et al., 2006a). LTP was markedly attenuated in the STZ+SE group, followed by the NS+SE group. We also used a simulation model to evaluate intracellular ATP and neuronal excitability and we found increased intracellular ATP concentration promoted action potential firing.

From our animal study, we found that compared with non-diabetic rats, diabetic rats were more susceptible to seizures, had higher SE-related mortality, performed significantly worse on hippocampus-dependent behavioral tests, lost more hippocampal neurons during the acute stage after SE, and exhibited an impaired LTP after SE. This finding suggests the importance of intensively treating hyperglycemia and seizures in diabetic patients with epilepsy (Huang et al., 2009).

SE-induced damage and network reorganization in lithium-pilocarpine-treated rats occurs as a consequence of neuronal loss and SE-induced sprouting (Lehmann et al., 2001). In addition to SE-related excitotoxicity (Curia et al., 2008), DH plus SE may amplify the adverse effects of hyperglycemia on neurons, both the direct effects and the indirect effects, such as diabetic oxidative stress (Vincent et al., 2007; Zupan et al., 2008), microvascular changes (Mraovitch et al., 2005; Qiu et al., 2008), and altered calcium homeostasis (Raza et al., 2004; Biessels et al., 2005). Because neuronal glucose uptake depends on the extracellular concentration of glucose, cellular damage can ensue after persistent episodes of hyperglycemia (Tomlinson and Gardiner, 2008). Diabetes may induce morphological changes in the presynaptic mossy fiber terminals that form excitatory synaptic contacts with the proximal CA3 apical dendrites (Magariños and McEwen, 2000).

Although impaired, synaptic plasticity is still present in animals with pilocarpine-induced epilepsy (Trudeau et al., 2004). The post-SE water maze analyses showed the STZ+SE group, followed by the NS+SE group, performed significantly worse than the other two groups. These findings again suggest the great negative impact of concomitant DH and SE on cognition, indicating that these two conditions interact in the brain. It has been suggested (Trudeau et al., 2004) that LTP deficits in diabetes might arise from dysfunction of the N-methyl-D-aspartate (NMDA) subtype of glutamate receptors in the early stages of the disease. In addition, loss of LTP maintenance in STZ-treated rats has been suggested to be a result of disrupting the calcium-dependent process modulating post-synaptic alpha-amino-3-hydroxy-5-methylisoxazole propionic acid (AMPA) receptors (Chabot et al., 1997). The aggravating effect of SE on the glutamatergic system, supported an additional effect of DH on worsening LTP (Pitsch et al., 2007).

One of the empirically based clinical guideline for treating SE is to give glucose immediately (Chen and Wasterlain, 2006). Our study suggests that physicians pay attention to glucose management when encountering concomitant SE and DH. Because seizure clustering and SE in DH are frequently seen in clinical practice, we advocate intensively treating hyperglycemia and seizures in this special population.

4. Epileptic seizures in diabetic hyperglycemia: A mechanistic view

The mechanisms underlying hyperglycemia-increased neuronal excitability remains incompletely understood. As a coupling of metabolism to membrane electrical activity, Adenosine triphosphate (ATP)-sensitive K^+ channels (K_{ATP}) is an important regulator of neuronal excitability and neuroprotection in metabolic stress, such as DH (Liss and Roeper, 2001; Seino and Miki, 2003). The direct connection between the level of electrical activity and intracellular ATP concentration suggests K_{ATP} potential for an antiepileptic role. The physiological regulation of K_{ATP} during metabolic inhibition involves protein kinase C-mediated K_{ATP} internalization to lessen the action potential duration shortening (Hu et al., 2003). Whether the epileptic circuit in individuals with DH involves K_{ATP} functional adaptation need further investigation.

K_{ATP} exist in many excitable cells, including cardiac myocytes, pancreatic β cells, muscle cells, and neurons (Liu et al., 1999, Seino, 1999). In pancreatic β cells, these channels are known to couple cellular metabolism to electrical activity by opening and closing as the intracellular ATP/ADP ratio decreases and increases, respectively (Ashcroft and Gribble, 1998). They are octameric complexes composed of four pore-forming units with inward rectifying characteristics (Kir 6.1 or Kir 6.2) and four sulfonylurea (SUR) binding sites (SUR1, SUR2A, or SUR2B) (Shyng and Nichols, 1997), regulated by intracellular ATP as well as pharmacological agents (e.g., diazoxide). These channels are highly responsive to changes in intracellular ATP levels generated during glucose metabolism. Rising levels of intracellular ATP close the K_{ATP} leading to depolarization and firing (Rowe et al., 1996; Ashcroft and Gribble, 1998). When the [ATP]/[ADP] ratio decreases, SUR1 and Kir 6.2 interaction reduces the latter's affinity for ATP, thereby opening the K_{ATP} .

In pancreatic β cells, elevation in blood glucose and the closure of K_{ATP} trigger events leading to calcium influx, cellular depolarization, and insulin secretion (Miki and Seino, 2005). In the CNS, K_{ATP} exist in many tissues, particularly the hippocampus and neocortex (Dunn-Meynell et al., 1998). Except for a similar role in sensing central glucose in hypothalamic glucose-responsive neurons (Miki et al., 2001), they are not involved in

specific neuroendocrine functions. Therefore, a more general role for these channels, functionally expressed in neurons, needs be investigated. In the brain, cells containing Kir 6.2 mRNA are widely distributed (Dunn-Meynell et al., 1998). A striking overlap with SUR1 mRNA suggests that the Kir 6.2/SUR1 complex is the best candidate for the brain functional K_{ATP} (Zawar et al., 1999; Betourne et al., 2009).

Owing to the abundant expression of K_{ATP} in the brain (Hicks et al., 1994; Mourre et al., 1990), the activation of K_{ATP} during ATP-depleted conditions has become a subject of studies. Mice lacking Kir6.2 (Kir 6.2 (-/-) mice) are vulnerable to hypoxia, exhibiting a reduced threshold for generalized seizure (Yamada et al., 2001). Transgenic mice, overexpressing the SUR1 gene in the forebrain, show a significant increase in the threshold for kainate-induced seizures (Hernandez-Sanchez et al., 2001). However, with excessive extracellular glucose and ATP in the hippocampal neurons, how K_{ATP} react is still marginally understood.

We hypothesized increases in extracellular glucose and intracellular ATP would attenuate K_{ATP} , with cells becoming more depolarized, leading to a more excitable state in hippocampal neurons. Thus, we investigated the effects of higher extracellular glucose on hippocampal K_{ATP} channel activities and neuronal excitability by using the cell-attached patch clamp configuration on cultured hippocampal cells (H19-7 cells) and the multi-electrode recording system on hippocampal slices. We found that incremental extracellular glucose could attenuate the activities of hippocampal K_{ATP} channels. Glucose significantly attenuates K_{ATP} channel activity in a concentration-dependent manner, mainly through a decrease in open probabilities. Higher levels of extracellular glucose could enhance neuropropagation which could be attenuated by diazoxide, a K_{ATP} channel agonist. Additionally, we found high levels of intracellular ATP, enhanced the firing of action potentials in model neurons. The stochastic increases in intracellular ATP levels also demonstrated an irregular and clustered neuronal firing pattern. Thus, this phenomenon of K_{ATP} channel-attenuation could be one of the underlying mechanisms of glucose-related neuronal hyper-excitability and propagation (Huang et al., 2007) (Figure 1).

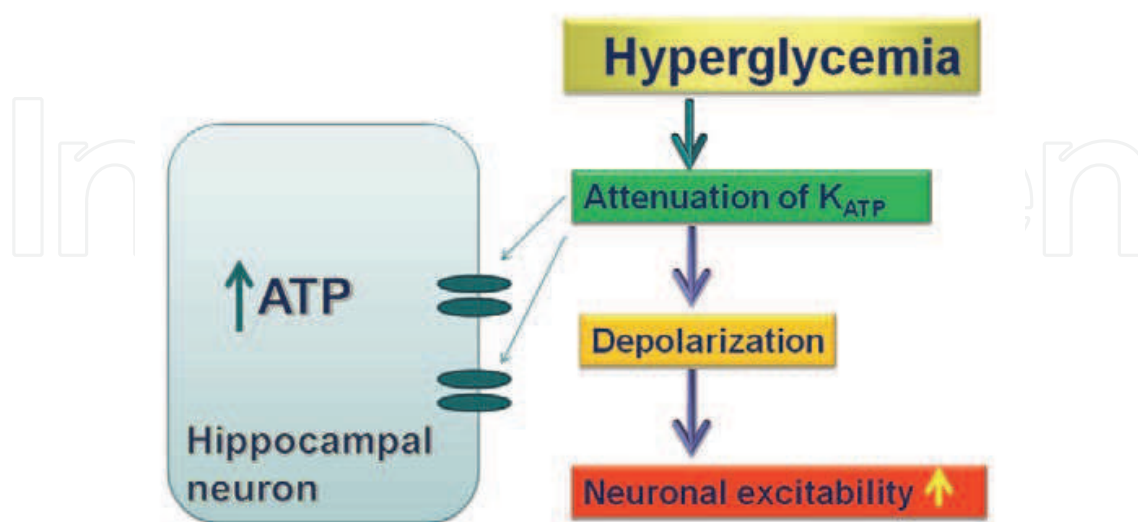


Fig. 1. The scheme of potential role of K_{ATP} underlying epileptic seizures in diabetic hyperglycemia.

From our study, we found glucose could enhance propagation through inhibition of K_{ATP} channel activity. The single-channel conductance, open-time, channel-bursting, ATP-sensitivity and voltage-insensitivity observed in these H19-7 cells were nearly identical to those described in native pancreatic β cells (Kir 6.2/SUR1) (Mukai et al., 1998). Despite the heterogeneous expression profiles of K_{ATP} channel subunits reported in hippocampal pyramidal neurons (Zawar et al., 1999), our study emphasized the role of β -cell type K_{ATP} channel in the hippocampus.

The effect of glucose on propagation has been suggested to be related to post-synaptic NMDA receptor activities (Abulrob et al., 2005). We implies the novel role of K_{ATP} channels. The increment in glucose leads to attenuation of K_{ATP} channel activities which would enhance field effects of EPSP, potentially caused by electrotonic spread of depolarization. Both pre- and post-synaptic K_{ATP} channels were involved in the electrical coupling effects in neurons (Matsumoto et al., 2002). Our study could support the role of post-synaptic K_{ATP} channel in neuropropagation, as there were more dominant effects on fEPSP with a relatively limited effect on pre-synaptic fiber volley and paired-pulse facilitation, in the presence of high glucose concentration.

The concentration-dependent attenuation of glucose on K_{ATP} -channel activity also aids in understanding the higher seizure susceptibility in higher degrees of hyperglycemia. Moreover, the stochastic simulation in this study suggested that in a state of intracellular ATP fluctuation, the neuronal firing pattern would show irregularity. This could be in parallel with the clinical situation where hyperglycemia-related seizures might develop as a result of paroxysmal action potential development in a steady state of hyperglycemia.

5. The therapeutic point-of-view on epileptic seizures in metabolic syndrome

As we investigated, the important metabolic couplers to electrical activity, K_{ATP} are potential mechanistic candidates when we treat these seizures (Figure 1). For clinical application, we started from the current available AEDs and we found there have been a few reports concerning the effects of Pregabalin (PGB), a newer AED, on some modulating effects on voltage-gated potassium channel (McClelland et al., 2004). Gabapentin-lactam, the derivative of gabapentin, has been found to exert an opening effect on K_{ATP} on the mitochondria (Pielen et al., 2004), which is a role in neuroprotection, added to the reduction of neuronal excitability. Moreover, it has been demonstrated that gabapentin can inhibit K^+ -evoked [3H]-noradrenaline release through the activation of K_{ATP} in both rat hippocampal and human neocortical cortex (Freiman et al., 2001). However, studies regarding the effects of PGB on K_{ATP} are still lacking.

We thus conducted an in vitro cellular study to investigate the effect of PGB on the activity of K_{ATP} present in H19-7 neurons. The inside-out configuration of the patch-clamp technique was employed to investigate K_{ATP} channel activities. Interestingly, PGB significantly opened these K_{ATP} channel activities in a concentration-dependent fashion with an EC_{50} value of 18 μM . There was a significant increase in the mean open-life time of K_{ATP} channels in the presence of PGB.

This study suggests that in differentiated hippocampal neuron-derived H19-7 cells, the opening effect on K_{ATP} channels could be one of PGB's underlying mechanisms in the reduction of neuronal excitability (Huang et al., 2006b). It's a novel finding regarding the mechanisms of PGB. Of interest, PGB applied to the intracellular surface of the excised

patches is able to activate K_{ATP} channels in these cells, suggesting that its binding site could be primarily on the intracellular leaflet.

The opening of K_{ATP} channels has been noted as neuroprotective, especially the β -cell-type K_{ATP} channels comprised of Kir6.2 and SUR1 (Yamada et al., 2001). Therefore, it is conceivable that the activation of K_{ATP} channels by PGB is anti-epileptic and potentially neuroprotective. PGB has been shown to rapidly penetrate the blood-brain barrier in pre-clinical animal studies (Ben-Menachem, 2004). In PGB treatment (600mg/d) for epilepsy, the usual therapeutic concentration range is around 2.8-8.2 mg/L (\approx 15-43 μ M) at steady state (Berry et al., 2005). From our study, the EC_{50} for PGB in opening K_{ATP} channel activities is around 18 μ M. From this point, it appears that the clinically relevant concentration would be similar to the concentration noted in our study.

Although we have shown (Huang et al., 2007) that, in *in vitro* hippocampal neurons, K_{ATP} agonists lead to membrane hyperpolarization and attenuate action-potential firing when extracellular glucose concentrations are high, there were no *in vivo* studies on whether K_{ATP} agonists protect against seizure severity and consequent SE-induced hippocampal damage in rats with DH. In addition, the functional relationship between Kir 6.2 and SUR1 in DH-related seizures remains unclear. We hypothesized diazoxide is protective in diabetic rats with SE, and, if so, whether the opening of K_{ATP} mediates this protection. K_{ATP} openers, including diazoxide, protect beta cells (Kir 6.2/SUR1) and preserve human and rat islets in high concentrations of glucose (Björklund et al., 2004; Maedler et al., 2004). Molecular and electrophysiological studies (Miki et al., 2001; Bancila et al., 2005; Sun et al., 2006; Huang et al., 2006b) report that Kir 6.2/SUR1 channels, like pancreatic beta cells, seem to be the dominant K_{ATP} isoform in the brain. It is thus reasonable to hypothesize that diazoxide protects CNS neurons.

In this study, adult male Sprague-Dawley rats (150-200g) were divided into two groups: the STZ-induced diabetes (STZ) group and the normal saline (NS) group. Both groups were treated with either diazoxide (DZX, 15 mg/kg, i.v.) (STZ+DZX, NS+DZX) or vehicle (STZ+V, NS+V) before lithium-pilocarpine-induced SE. We evaluated seizure susceptibility, severity, and mortality. The rats underwent Morris water-maze tests and hippocampal histopathology analyses 24 hours post-SE. Similar to previous studies, a multi-electrode recording system was used to study fEPSP. Seizures were less severe, post-SE learning and memory were better, and neuron loss in the hippocampal CA3 area was lower in the STZ+DZX than the STZ+V group. In contrast, seizure severity, post-SE learning and memory, and hippocampal CA3 neuron loss were comparable in the NS+DZX and NS+V groups. fEPSP was lower in the STZ+DZX but not in the NS+DZX group. In addition, RNA interference (RNAi) to knockdown Kir 6.2 in a hippocampal cell line was used to evaluate the effect of diazoxide, in the presence of high concentration of ATP. The RNAi study confirmed that diazoxide, with its K_{ATP} -opening effects, could counteract the K_{ATP} -closing effect by high dose ATP. We conclude that, by opening K_{ATP} , diazoxide protects against SE-induced neuron damage during DH (Huang et al., 2010).

We showed *in vivo* and *in vitro* evidence that diazoxide indeed protected STZ diabetic rats against SE-induced hippocampal damage. There are reports (Mattia et al., 1994; Yamada et al., 2001; Soundarapandian et al., 2007) that modulated K_{ATP} may alter the seizure threshold and epileptiform activity in hippocampal slices in rats. Nevertheless, this class of compounds has not yet been generally effective in some animal models, such as the maximal electroshock model, the kindling model (Wickenden, 2002), and in our NS rats.

[³H] glyburide binding to SUR receptors in the brain appears to be generally upregulated in the state of hyperglycemia (Levin and Dunn-Meynell, 1998). In rats with DH, diazoxide opened K_{ATP} , which were frequently attenuated in a state of high extracellular glucose concentration (Huang et al., 2007). Diazoxide reduced glutamate release by opening presynaptic K_{ATP} Kir 6.2/SUR1 channels (Bancila et al., 2004). As diazoxide activates K_{ATP} by interacting with the SUR1 subunit (transmembrane domain 1 and nucleotide binding domain 1) (Nichols, 2006), opening K_{ATP} is potentially beneficial in a seizure during hyperglycemia.

The hippocampus is rich in Kir 6.2/SUR1-based channels (Thomzig et al., 2005; Sun et al., 2006). Hippocampal K_{ATP} are involved in processing new information at the mossy fiber CA3 synapses (Quinta-Ferreira and Matias, 2005). Reports (Zarrindast et al., 2006; Betourne et al., 2009) on the effect of diazoxide on contextual memory, however, are inconsistent. During learning, as the energy demand increases, mossy fiber K_{ATP} may sense a rise in intracellular ATP, which closes the K_{ATP} and increases glutamate release. Conversely, K_{ATP} that open immediately after intense electrical activity may also protect CA3 cells from glutamate-mediated excitotoxicity (Betourne et al., 2009). Based on our water-maze and pathology results, diazoxide -induced opening of K_{ATP} counteracted SE-related excitotoxicity in STZ rats.

6. Conclusion

Diabetic hyperglycemia might aggravate seizures. An aggressive search for diabetic hyperglycemia and intensive control of glucose in new onset seizures are helpful in management. The outcome of seizures is probably more deteriorating in diabetic patients with epilepsy. Because seizure clustering and status epilepticus in diabetic hyperglycemia are frequently seen in clinical practice, we advocate intensively treating hyperglycemia and seizures in this special population.

Our study provides more direct mechanistic evidence that increments of central neuron excitability, in a state of high glucose levels, can be attributed to K_{ATP} channel activity attenuation. K_{ATP} agonists are worth investigating as treatments for epileptic seizures in diabetic hyperglycemia.

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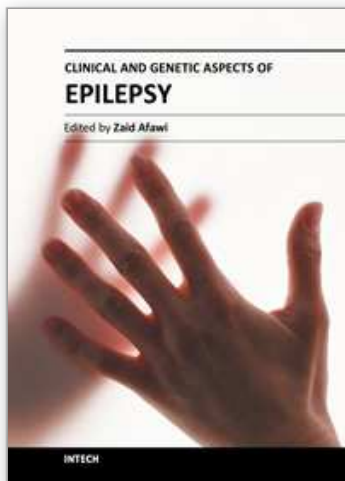
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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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InTech China

Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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