Clinical Study

What Do Changes in Brain Perfusion Induced by Etomidate Suggest about Epilepsy in Human Patients?

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Epilepsy is one of the major neurological disorders, affecting roughly 1-2% of the world's population, of which approximately 20–25% of patients are drug resistant. A variety of drugs have been used to activate and identify the epileptic area in patients during presurgical evaluation. We studied the cerebral blood flow (CBF) by single photon-emission computed tomography (SPECT) and bioelectrical brain activity responses to etomidate in 11 patients. Etomidate (0.1 mg/kg) was administered while patients were monitored by video-electroencephalography with foramen ovale electrodes (FOEs). After etomidate administration, a brief period of high-frequency activity was observed, followed by a generalized, high-voltage delta pattern. Increased regional CBF was observed bilaterally in thalamus, putamen, and posterior hippocampus. Besides, the only interhemispheric difference was observed in the posterior hippocampus, where CBF decreased in the epileptic temporal lobe. Activation by etomidate induces a specific and repetitive response in the bioelectrical activity. In addition, CBF changes induced by etomidate may serve as a diagnostic tool in the near future.

1. Introduction

Epilepsy affects 1–2% of the population worldwide and can be considered one of the most prevalent neurological illnesses [1]. Furthermore, between 20 and 25% of epileptic patients are resistant to drug treatment [2]. The most common type of drug-resistant epilepsy is temporal lobe epilepsy (TLE); however, patients with this form of epilepsy might be candidates for surgical resection of the epileptic focus [3, 4]. Before surgical resection, patients undergo a battery of tests during presurgical evaluation, including noninvasive ancillary tests such as video-electroencephalography (v-EEG), magnetic resonance imaging (MRI), single photon emission-computed tomography (SPECT), and positron emission tomography (PET) [3–5].

On occasion, invasive recordings are required, among which are foramen ovale (FOE), subdural, or depth electrodes [2].

SPECT is a technique that measure the regional cerebral blood flow (CBF) using radio-tracers [6, 7], and it can be used during ictal or interictal phases. Ictal SPECT is considered useful for identifying the epileptic zone (EZ, defined as the anatomical area necessary and sufficient for initiating seizures, and whose removal or disconnection is necessary for abolition of seizures), which is usually associated with regional hyper perfusion. On the other hand, the interictal SPECT is not performed regularly, but when performed the epileptogenic area shows hypoperfusion [8].

Alternatively, a pharmacological approach can be taken to identify the EZ. For this purpose, several different drugs

have been used, including methohexytal [9], clonidine [10], etomidate [11], pentylenetetrazol [12], thiopental [13], and the opiates fentanyl and alfentanyl [14]. However, the search for an appropriate pharmacological agent for EZ identification is far from complete because nonspecific responses often result and because poorly tolerated side-effects preclude the safe use of many drugs (e.g., the stiffness induced by opiates).

An ideal drug for EEG activation should have the following features: (1) it should be well tolerated by the patient, with a fast onset and rapid decline of activity, as well as a low level of side-effects, (2) it should produce selectively increased activity in the epileptic zone, implying no new interictal epileptiform discharges (IEDs) emerging, and (3) it should specifically distinguish between the interictal zone (IZ, the area showing interictal epileptiform discharges or IED) and ictal onset zone (IOZ, where seizures in fact start) [15].

Etomidate is a rapidly-inactivating imidazol derivative [sulphate-R-(+)-ethyl-1-(-1-phenylethyl)-1-H-imidazol-5-carboxylate] with a peak effect at 1 min and a duration of 3–5 min. It is a nonbarbiturate hypnotic agent without analgesic properties but does activate gamma-aminobutyric acid A (GABA$_A$) receptors [16]. One important benefit of etomidate is its safety; the lethal dose is 30 times greater than the effective dose. Although etomidate has been sporadically used for EEG activation [17, 18], to date, no systematic studies on the effect of etomidate on CBF have been performed.

The central aims of this study were to analyze changes in regional CBF in patients with TLE in response to administration of etomidate and to examine its possible utility for diagnosis during presurgical evaluation.

2. Material and Methods

2.1. Patients. The present study included 11 patients (5 women, 6 men) who were diagnosed with intractable epilepsy of the mesial temporal lobe. Informed consent was obtained from all patients and were studied according to an approved protocol used by the Epilepsy Surgery Unit at La Princesa Hospital [3, 4]. This research was approved by the Hospital Ethical Committee. The mean age of the patients was 28.8 ± 2.8 years (x ± SEM) for men and 33.6 ± 3.0 years for women, and men and women had a history of epilepsy for 14.3 ± 4.7 years and 23.2 ± 5.4 years, respectively. Clinical data from patients are shown in Table 1.

Patients were evaluated presurgically using the following: (1) 19-channel scalp EEG according to the 10–20 international system, (2) interictal SPECT using ^{99m}Tc-HmPAO, (3) 1.5 T MRI, and (4) v-EEG with 19 scalp electrodes positioned according to the international 10–20 system and complemented with FOEs [5]. In all patients, a neuropsychological and psychiatric evaluation was performed.

The EZ includes the IZ, where IEDs appear, and IOZ. The IOZ was defined as the region where the seizures originated according to the v-EEG + FOE recording. In this study, the EZ (especially when assessed with SPECT) and IOZ were equivalent (i.e., we do not differentiate between irritative and ictal onset zone in SPECT studies).

During the v-EEG recording, antiepileptic drugs were removed from the second to the fourth day of the test. To evaluate etomidate, the drug was administered intravenously (i.v.) between the second to the third day in the v-EEG unit.

2.2. Etomidate Perfusion. Etomidate (Janssen-Cilag, Spain) was administered i.v. at a dose of 0.1 mg/kg under quiescent conditions, with the patient resting supine in bed while under continuous supervision by an expert anaesthesiologist (MLM, JLM-Ch, ED). Supplementary oxygen was administered through nasal goggles at 5 L/ min rate. The electrocardiogram (EKG), capillary oxygen saturation (SaO$_2$), and respiration rate (RR) were continuously monitored during the evaluation. Electrical brain activity was monitored by v-EEG + FOE.

2.3. Cerebral Perfusion. Regional CBF was evaluated by SPECT imaging. A bolus of ^{99m}Tc-HmPAO (740 MBq) was intravenously injected immediately after etomidate administration (see Pastor et al., 2008). Studies were performed using a low-energy high-resolution collimator, a simple-head camera (Starcam 3200, General Electric), and 96 projections of 22 s each, using a 64 × 64 matrix. Slices were reconstructed by filtering back projections using a Butterworth filter (order 10 with a 0.6 cut-off). The brain SPECT images were acquired in the 30 min following the complete recovery of the patient after etomidate administration.

Quantitative analysis of brain perfusion was performed using NeuroGam software (General Electric) to compare several areas of interest, including the frontal, temporal, parietal, and occipital lobes, the putamen, globus pallidus, and thalamus, as defined by default by the software. Moreover, we defined the following areas according to the Talairach-Tournoux atlas (1998): the latero-basal temporal cortex, amygdaloid body, anterior hippocampus, and posterior hippocampus.

To evaluate changes in CBF, we defined the Δ as

$$\Delta = \text{CBF}_{etom} - \text{CBF}_{basal}, \tag{1}$$

where CBF_{etom} and CBF_{basal} are measures of regional CBF after etomidate administration and under basal conditions, respectively. Basal SPECT was performed approximately either one week previous or one week after the etomidate activated one.

2.4. Statistical Analysis. Statistical comparisons between groups were performed using the Student's *t*-test (parametric samples) or the Mann-Whitney Rank sum test (nonparametric samples) if normality failed. Significant changes in regional CBF (Δ) were assessed using the z-score, according to the following (null and alternative) hypotheses:

$$\text{H}_0 : \mu_1 = 0 \qquad \text{H}_1 : \mu_1 \neq 0. \tag{2}$$

Statistical analyses were performed with SigmaStat 3.5 software (Point Richmond, USA). The significance level was set at $P < .05$. Results are shown as mean ± SEM unless otherwise indicated.

TABLE 1: Clinical features of patients.

Patient	Sex	Age (years)	History (years)	Basal SPECT	Seizure type	MRi	v-EEG + FOE	Surgery/Engel's grade
1	F	38	18	Left mes temporal	Partial complex	Normal	Left- Mesial Temporal	L AMTR/ I
2	F	39	34	Bi-T (L > R)	Partial complex	Right MS	Right mesial	R AMTR/ I
3	F	35	33	Left mes temporal	Partial complex	Left MS	Left mesial	L AMTR/ I
4	M	25	9	Left mes temporal	Partial simple & complex	Left parasellar cyst	Left mesial	L AMTR/ I
5	F	22	5	Left temporal Left F-P	Secondary Generalized	Normal	Left mesial	L AMTR/ I
6	M	38	37	Bi-T mes (Left > Right)	Partial complex	Left MS	Left mesial	L AMTR/ I
7	M	21	5	Right mes temporal	Partial complex	Normal	Right mesial	R AMTR/ I
8	M	30	11	Right mes	Partial complex	Left MS	Bi-T (Left > Right)	#L AMTR/ IV
9	M	36	13	Left mes temporal	Partial complex	Normal	Left mesial	L AMTR/ II
10	F	34	26	Left Mesial temporal	Partial complex	Normal	Left mesial	No surgery
11	M	23	11	Left Mesial temporal	Partial complex	Normal	Left mesial	L AMTR/ I

AMTR: anterior medial temporal resection; Bi-T, Bi-temporal; F: female; F-P: fronto-parietal; L: left; M: male; mes: mesial; MS: mesial sclerosis; R: right. Engel's grade [19] at least one year after surgery. #This patient showed two seizures from left mesial temporal lobe and one seizure from right mesial temporal lobe. The operation was palliative.

3. Results

3.1. Clinical Effects Induced by Etomidate.
Intravenous administration of etomidate to awake patients was performed over a period of 32.4 ± 2.8 s. Progressive drowsiness occurred in 5 patients, while only 1 patient showed severe and rapid drowsiness. In 4 patients, no clinical signs of sleep were observed. In the majority of patients (7), mild myoclonus was observed, especially in the mouth, eyelids, and distal muscles of the upper extremities. One patient showed severe myoclonus in the right arm, which was not associated with ictal activity. In 3 patients, there was no sign of myoclonia. In 2 cases, the patients described a moderate and localized pain in the arm during etomidate administration. This pain resolved within a few seconds of completing the etomidate injection.

All patients recovered in less than 10 min and did not require any special care.

Administration of etomidate produced no changes in SaO_2, heart rate measured by EKG, or RR.

3.2. Bioelectrical Activity Induced by Etomidate.
Shortly after completion of etomidate administration, small increases in the amplitude and frequency were observed in the scalp EEG (stage 1), followed by generalized, large-amplitude delta activity (stage 2). This pattern was similar to that described previously for nonepileptic subjects [20, 21]. High-voltage spikes and sharp-waves (clearly different from the background activity) increased their frequency (spikes/min) in mesial and, in a lesser degree, in temporal lateral areas, compared with basal activity. It is important to consider that IED only appeared in those areas where spikes were recorded under basal conditions (Figure 1).

Taking into account the short latency of changes in EEG and the dynamics of brain activity after etomidate injection, we can assume that almost a 40% of ^{99m}Tc-HmPAO is in the brain [6] when the EEG activity is in stage 2.

Therefore, etomidate induced a specific pattern of brain activity, which included nonirritative activity on the majority of scalp leads, in addition to irritative activity specifically over those areas where IEDs previously were observed.

3.3. Effects of Etomidate onto the Cerebral Perfusion.
We measured the changes in CBF induced by etomidate. We observed a significant increase in the regional CBF in the thalamus ($P < .05$, z-score, n = 22), the posterior hippocampus ($P < .05$), and putamen ($P < .05$), and these changes occurred bilaterally. However, the only brain structure in which the regional CBF differed between epileptic and nonepileptic hemispheres was the posterior hippocampus (Figure 2). In this area, a CBF was significantly increased in the nonepileptic lobe compared with the epileptic lobe ($P < .05$, paired Student's t-test).

It is interesting to consider the activation mediated by etomidate in the mesial temporal region because we would expect to find an increase in CBF associated with increased interictal activity.
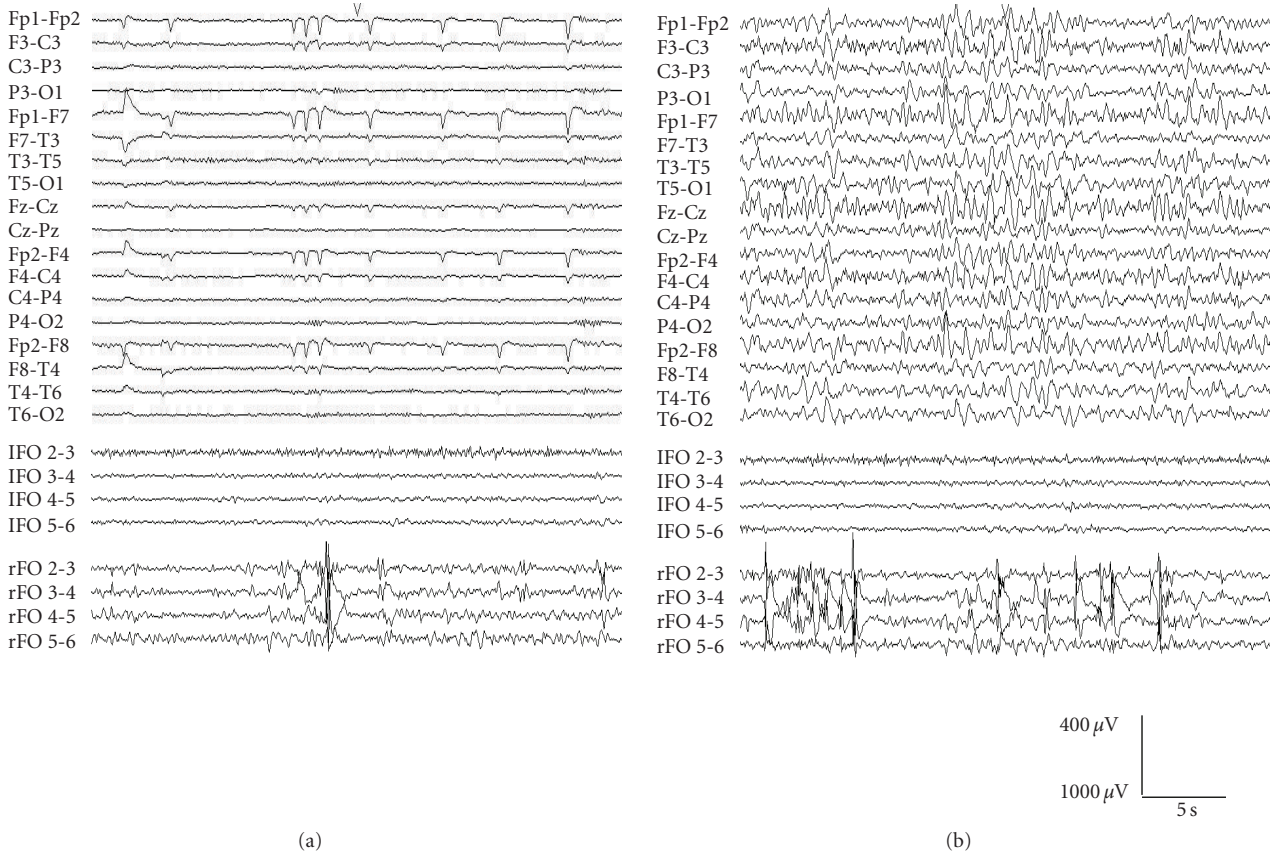
FIGURE 1: Bioelectrical brain activity induced by etomidate. (a) Scalp and FOE recording in basal conditions, 1 minute previous to etomidate administration. (b) Activity recorded 1 minute after etomidate. Slow high-amplitude activity is observed widespread in scalp, specially in anterior regions. It is important to note that IEDs appear in the same region where the spontaneous seizure originated.

4. Discussion

In this study, we have shown that administration of etomidate is a safe and efficient pharmacological method potentially useful in patients suffering from TLE during presurgical evaluation. However, the changes observed in regional CBF, specifically in areas associated with the EZ, have been unexpected.

Traditionally, several different drugs are used to induce brain activity. As stated previously, it is clinically important that side effects induced by a drug be well tolerated by the patient [15]. As we have demonstrated, this is the case for etomidate. The primary side effects observed were myoclonus and moderate pain.

The appearance of myoclonus following etomidate perfusion has previously been described [16]. Although these events are not associated with epileptic activity measured by scalp recordings, a medullar origin for myoclonic movements has been proposed [22, 23]. Significantly, etomidate has been described as a very safe hypnotic [16]. In fact, no significant hemodynamic effects have been observed [24], although higher doses (0.35 ± 0.17 mg/kg) have been shown to induce tachycardia and increase mean arterial pressure [21].

As previously reported [17, 21, 25], etomidate leads to a brief increase in amplitude and frequency of brain activity, recorded by scalp EEG, followed by generalized high-voltage delta activity. The latter activity resembles that seen during nonrapid eye movement (NREM) delta sleep. Etomidate is a potent GABA agonist, and GABA plays an important role in NREM delta sleep [26, 27]. These evidences may explain the increased thalamic regional CBF induced by etomidate. We cannot exclude, however, that increases in CBF in the basal ganglia might be related to ictal patterns in epileptic patients [28].

Traditionally an intense increase in regional CBF is one of the hallmarks of partial-onset seizures. This is probably due to an increase in regional synaptic activity and changes in neurotransmission. During the ictal SPECT, the ^{99m}Tc-HMPAO infusion is performed briefly after the seizure starts and, moreover, a delay must be overcome before the radiotracer gets to the brain. So, ictal SPECT, probably shows an increase in regional cerebral perfusion that is surely related to the seizure [29] but is almost certainly indicating propagation from the area of ictal onset.

The relative decrease in regional CBF observed in the posterior hippocampus of EZ was a surprising result. Instead, we expected an increase in regional CBF in the IOZ, taking
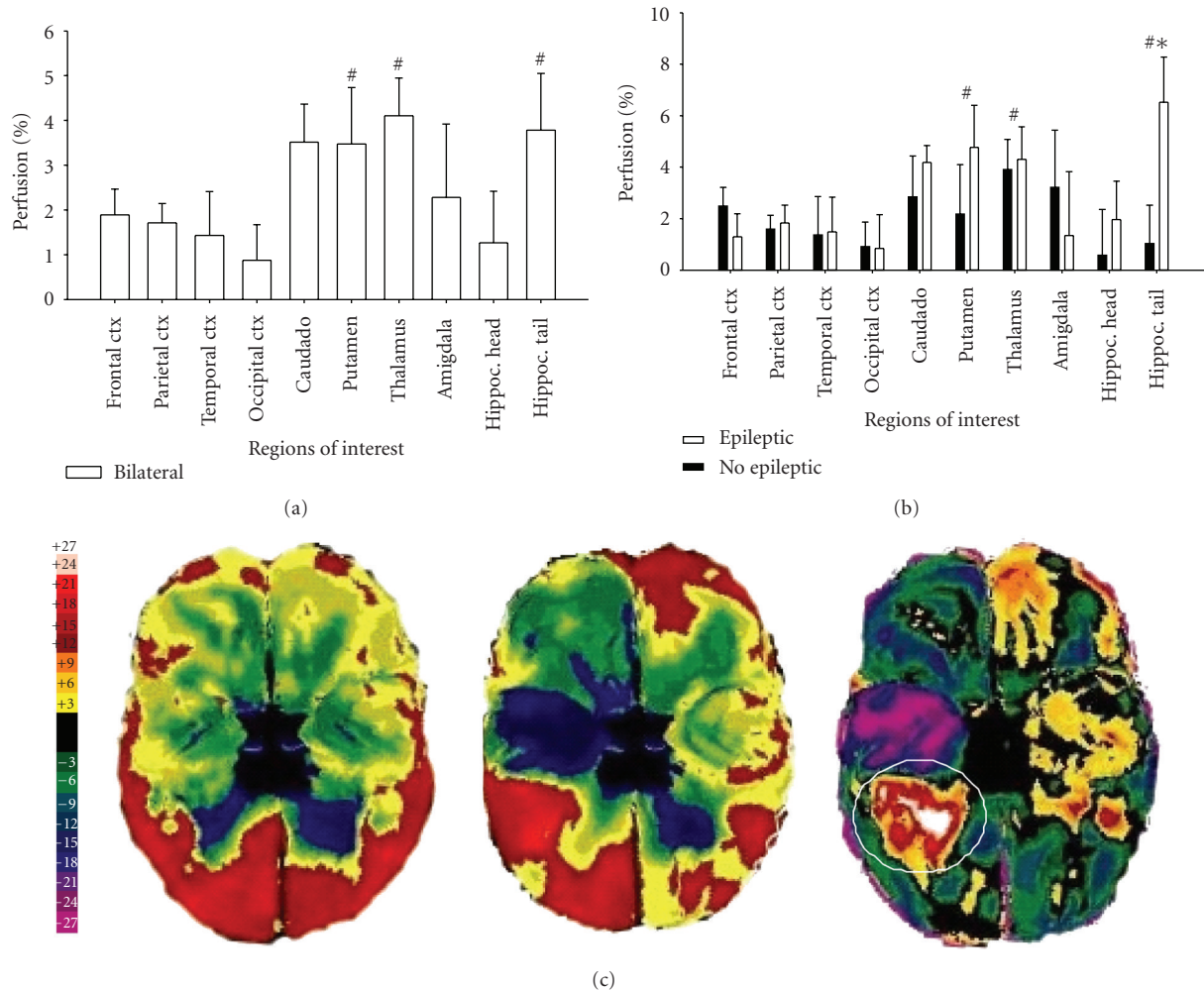
FIGURE 2: Effects of etomidate on CBF. (a) Graph showing the global pattern of changes induced by etomidate, considering cerebral regions from both hemispheres. (b) Graph summarizing the CBF changes by etomidate in regions pertaining to the epileptic hemisphere (black box) and nonepileptic hemisphere (empty box). (c) Ventral view of different brain SPECTs in the same patient, during basal condition (left) and when activated by etomidate (middle). The image on the right corresponds to the substraction of the two previous images. The circle shows the increase in regional CBF in the right posterior mesial area. $^{\#}P < .05$, z-score test ($n = 22$).$^{*}P < .05$, paired Student's-t-test ($n = 11$ pairs).

into account the significant increase in the IED induced by etomidate. Recently, it has been demonstrated that in the sclerotic hippocampus there is a consistent and highly significant reduction of micro-blood vessels, particularly in the CA1 field [30]. This reduction could be related to the relative inability of the epileptic posterior hippocampus to increases CBF locally in response to etomidate. On the other hand, one could also hypothesize that etomidate increase the CBF more significantly in the structures spared by epileptic discharges. Although we are conscious of the necessity for further experiments in order to fully elucidate the mechanisms underlying etomidate-induced increases in CBF and brain activity, from a clinical point of view, our findings can be significant methods of presurgical evaluation.

In contrast to other anaesthetics, etomidate has a very specific target at clinical concentrations [31]. In fact, etomidate almost exclusively acts on the β_2 and β_3 subunits of the GABA$_A$ receptor. This specificity can be very important for diagnosis in presurgical evaluation. The exact mechanism by which etomidate activates the irritative area is not completely understood. However, several lines of evidence may explain this effect (Figure 3). Examination of slices obtained from epileptic patients has revealed a decrease in the reversal potential for Cl$^-$ anions [32]. This change could induce a depolarization instead of hyperpolarization following GABA release, thereby driving irritative activity.

On the other hand, studies in cultured astrocytes have shown that etomidate can inhibit glutamate uptake, increasing the extracellular glutamate concentration to such a level that can spill out of the synaptic cleft and activate extrasynaptic receptors. As a consequence, irritative activity would be increased [33].

We conclude that activation of bioelectrical activity and measurement of regional CBF in patients during presurgical
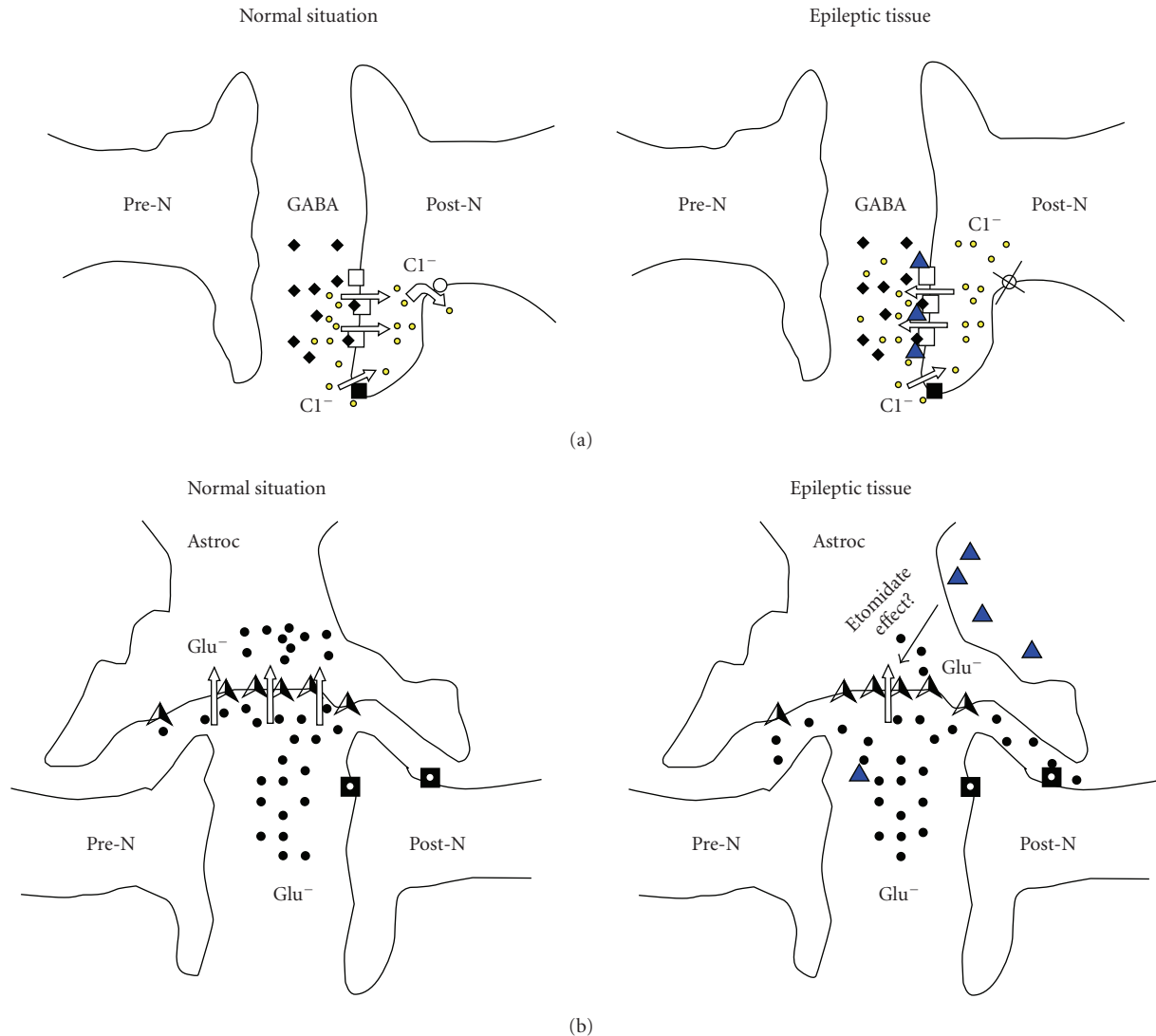
Normal situation

Epileptic tissue

(a)

Normal situation

Epileptic tissue

(b)

Figure 3: Theoretical mechanisms of etomidate effect on the epileptic activity. Astroc: astrocyte; pre-N: presinaptic neuron; post-N: postsinaptic neuron. (a) Reversal of Cl$^-$ potential. Here, $\lozenge$ represents GABA, $\square$ represents a GABA$_A$ channel, $\blacksquare$ represents NKCC1 (sodium-potassium chloride contransporter), $\circ$ represents KCC2 (potasium-chloride contransporter), $\bullet$ represents a chloride anion, and $\blacktriangle$ represents etomidate. (b) Reduced re-uptake of glutamate by astrocytes through EAAT1 and 2 (Excitatory aminoacid transport) due to etomidate action through protein kinase A (PKA) pathways where $\bullet$ represents glutamate, $\blacktriangle$ represents etomidate, $\succ$ represents EAAT 1 and 2, and $\blacksquare$ represents a glutamate channel.

evaluation could be of great utility in epilepsy units as a complementary test to increase the accuracy of diagnosis in patients being evaluated for TLE.

Abbreviations:

v-EEG: video-Electroencephalography;
FOE: Foramen Ovale Electrodes;
SPECT: Single Photon Emission Computed Tomography;
CBF: Cerebral Blood Flow;
EZ: Epileptogenic Zone;
IED: Interictal Epileptiform Discharges;
TLE: Temporal Lobe Epilepsy.

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