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Review article

# LPDs – «Linked to penumbra» discharges or EEG correlate of excitotoxicity: A review based hypothesis

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ABSTRACT

Periodic lateralized epileptiform discharges (PLEDs) or lateralized periodic discharges (LPDs) are a well-known variant of pathological EEG activity. However, the mechanisms underpinning the appearance of this pattern are not completely understood. The heterogeneity of the features derived from LPDs patterns, and the wide range of pathological conditions in which they occur, raise a question about the unifying mechanisms underlying these phenomena. This paper reassesses the current opinion surrounding LPDs which considers glutamate excitotoxicity to be the primary pathophysiological basis, and the penumbral region to be the main morphological substrate. Arguments in favour of this hypothesis are presented, with interpretations supported by evidence from recent literature involving clinical and experimental data. Presently, no single hypothesis places considerable emphasis on the pathochemical properties of LPDs, which are implicitly meaningful towards better understanding of the clinical significance of this pattern.

## 1. Introduction

The term periodic lateralized epileptiform discharges (PLEDs) was first introduced by Chatrian et al. 1964, while the term 'periodic', describing the corresponding changes in the electroencephalogram (EEG) was first applied by Cobb and Hill as early as 1950 (Chatrian et al., 1964; Cobb and Hill, 1950). The American Clinical Neurophysiology Society has proposed to replace the term periodic lateralized epileptiform discharges (PLEDs) to lateralized periodic discharges (LPDs), pointing out the questionable epileptogenic nature of this pattern (Hirsch et al., 2013). In this paper we follow these recommendations, applying «LPDs» both for LPDs and PLEDs regardless of their application in original publications. Periodic EEG changes are usually classified as LPDs, bilateral independent periodic discharges (BIPDs), or generalized periodic discharges (GPDs), with further subclassification including LPDs-proper and LPDs-plus. (Andraus et al., 2012; Garzon, 2012).

LPDs have long been recognized as abnormal findings in EEG signal although their clinical significance has not been clear (Lee, 2012). LPDs are an EEG pattern indicative of an acute (or less often subacute) nonspecific brain injury, which can be accompanied by seizures (Andraus et al., 2012), and are generally associated with poor prognosis, particularly in patients with neoplasms (Lee, 2012).

Lateralized periodic discharges have been reported to occur across all age groups, with the overall prevalence of LPDs ranging from 0.4–1 % with rare cases up to 1.44 % (Fitzpatrick and Lowry, 2007; Li et al., 2017).

LPDs are electrographically heterogeneous. They can be surface-negative, bi-, tri-, or polyphasic discharges consisting of spiking, sharp, polyspike components, alternating with slow-wave complexes of amplitude 50–1000 μV that last for 60–600 ms (mean 200 ms), usually occurring in the 0.5–4 Hz band (ranging from 0.1 Hz up to 5 Hz) (Kaplan, 2007; Freund and Kaplan, 2018). Oscillations with frequencies higher than 8 Hz are suppressed in the region of the LPDs and background activity between complexes is usually irregular and of low voltage (Young et al., 1988; Kate et al., 2012; Isobe et al., 2016).

Thus, LPDs are a well-known electroencephalographic phenomenon, but fundamental questions regarding their origin and clinical significance require further discussion and exploration. The pathochemical mechanisms underlying the LPDs generation are poorly described in the literature and lacking the common ground (Freund and Kaplan P.W., 2018; Lin and Drislane, 2018). A recent review by Lin and

*Abbreviations:* PLEDs, Periodic Lateralized Epileptiform Discharges; LPDs, Lateralized Periodic Discharges; BIPDs, Bilateral Independent Periodic Discharges; GPDs, Generalized Periodic Discharges

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Drislane presents some ideas regarding pathophysiological mechanisms underlying LPDs which are quite close to our hypothesis, though they are not in the main focus of this paper and are discussed in very general terms (Lin and Drislane, 2018).

## 2. Hypothesis

Until now, several seemingly unrelated features of LPDs have been described. Firstly, it has been reported that LPDs appear early on at the onset or episode of the disease exacerbation, anywhere within the first days or even in the first 24 h (Schwartz et al., 1973). Secondly, LPDs are persistent over relatively short periods, typically for several days and rarely more than 4 weeks (Kate et al., 2012). Thirdly, some authors have posited a potential relationship between LPDs and brain lesions dynamics (Chabolla et al., 1996; Isobe et al., 2016). Additional characteristics are described below. In this article, we aim to show that the factor integrating all of these features is related to glutamate excitotoxicity.

This article highlights the evidence supporting the hypothesis that LPDs reflect glutamate excitotoxicity (as a universal pathochemical process) occurring mainly in penumbral region of lesion.

## 3. Overview of evidence supporting the hypothesis

### 3.1. Etiological aspects

The assumption that LPDs may reflect localized hyperexcitability in the penumbral zone of ischemic stroke, has been expressed previously by Pohlmann et al. (Pohlmann-Eden et al., 1996). Further experimental investigations have demonstrated LPDs appearance over the penumbra zone in a model of focal cerebral ischemia (Hartings et al., 2006). Even though stroke remains the leading cause of LPDs, the etiological spectrum of this pattern is very wide (Fitzpatrick and Lowry, 2007).

Glutamate excitotoxicity is a final common pathway caused by brain injury due to various acute neurological conditions such as ischemic stroke, hypoxic-ischemic encephalopathy, herpetic encephalitis, traumatic brain injury, epileptic status, cerebral organic acid disorders, toxic or metabolic leukoencephalopathy, Creutzfeldt-Jakob disease, and multiple sclerosis (Moritani et al., 2005).

The penumbral zone appears to be a common component underlying various brain disorders, such as focal structural lesions in traumatic brain injury. Areas with reversible damage caused by spreading excitotoxicity, analogous to the ischemic penumbra, can be allocated to this lesion (Guerriero et al., 2015). Within the context of brain tumors, a peritumoral zone may be similar to the penumbra, as primary brain tumors have demonstrated a significant increase in the level of glutamate release from the tumor in peritumoral zone (Buckingham et al., 2011). This idea can be partially supported by recent experimental data from magnetoencephalography study, which showed that the source of periodic discharges does not lie directly in the core of the lesion, but arises from the perilesional regions (Shvarts et al., 2017).

Thus, expanding on theoretical notions regarding the penumbral zone and excitotoxic neuronal injury involved in its formation we can draw a conclusion that LPDs appearance may reflect this pathophysiological mechanism regardless of nosological affiliation. Further support to our hypothesis is provided by the fact that LPDs resolve considerably after the use of such antiepileptic drugs as felbamate, topiramate and perampanel, which block glutamate receptors (Hughes and Fuller, 1995; Perry et al., 2006; Rohracher et al., 2015).

### 3.2. Anatomical substrates of periodicity

One of the most essential features of LPDs is periodicity. Previous explanations for this phenomenon are mainly limited to emphasizing the types of lesion or anatomical substrates, which might generate LPDs (Lehmann et al., 1962; Cobb and Hill, 1950; Gloor et al., 1968; Cobb, 1979; Ergün et al., 2006).

Particular attention is paid to the generation and periodicity of LPDs in relation to subcortical structures, in particular to the thalamus (Gross and Quesney, 1998; Ergün et al., 2006; Katramados et al., 2009). A convincing argument for thalamus involvement in the formation of LPDs is given in the study of patients, who presented focal status epilepticus and thalamic abnormalities on diffusion-weighted magnetic resonance imaging within registration of LPDs. Thalamic hyperintense lesions on diffusion-weighted imaging appeared in the region of the pulvinar nucleus, ipsilateral to the epileptiform activity, according to nuclei projection to the occipital cortex (Katramados et al., 2009). However, it is worth noting, that ipsilateral focal thalamic hyperintense lesions can characterize the phenomenon of thalamic diaschisis.

Another substrate often observed in relation to LPDs, is the cerebellar lesion (Erkulvrawatr, 1977), notably the crossed cerebellar diaschisis. There have been several studies investigating LPDs association with the crossed cerebellar diaschisis (Fernández-Torre et al., 2007; Ahn et al., 2014; Stübgen, 1995; Baradaran et al., 2016). This type of injury is known to frequently accompany ischemic stroke (Komaba et al., 2004), but has also been described in cases of epilepsy, encephalitis and tumors (Mewasingh et al., 2002). This phenomenon is assumed to be caused by excessive neuronal activity from prolonged excitatory synaptic activity via the cortico-pontine-cerebellar pathways (Samaniego et al., 2010). The assumption about the cause-effect relationship between LPDs and cerebellar lesion is not obvious as it has not been rigorously proven. However, pathological changes in the cerebellum can facilitate an epileptiform activity probably due to the impairment of the GABAergic inhibition to the forebrain (Rubio et al., 2016; Vander et al., 2004).

### 3.3. Physiological substrates of periodicity

Periodicity of discharges could be explained by neuronal excitation in conditions of increased levels of glutamate. It has been previously shown that neurons of hippocampal culture survived after the glutamate exposure manifested spontaneous recurrent epileptiform discharges. Those neurons were considered to be the analogue of the ischemic penumbra (Sun et al., 2001; DeLorenzo et al., 2007). Another experimental model of neuronal discharge dynamics under conditions of abnormal astrocytic glutamate concentration described the peak of astrocytic glutamate level coinciding with a short period of depolarization block. Moreover, the phase of lower concentration of glutamate corresponded to the epileptic discharge (Li et al., 2016).

Interestingly, the models mentioned above closely align with earlier hypotheses which concluded that inter-discharge intervals (in the pattern structure) can reflect a long refractory period. The discharges themselves reflect a massive depolarization of neurons, which are repeatedly excited by unknown stimuli (Gloor et al., 1968; Hernández-Fernández et al., 2011). Glutamate is a suitable candidate for the role of such a stimulus.

The mechanism of discharge formation, whose amplitude is significantly greater than the amplitude of the background EEG activity in the penumbral area projection, is not entirely clear. The contribution of postsynaptic potentials to the discharge formation, which is described in particular for interictal epileptiform discharges, is highly questionable in the pathological conditions of the penumbra (Masherov, 2000; Sun et al., 2001; Bolay et al., 2002).

Presumably, an increase in the level of neuronal action potential synchronization in pathological regions could be considered the main phenomenon underlying the appearance of the discharges. Apparently, such synchronization should have the character of a non-synaptic mechanism. Increasing neuronal synchronization could be a consequence of periodic reversible increases of intracellular calcium concentration occurring as the result of NMDA receptor activation by glutamate released from glial cells (Carmignoto and Fellin, 2006).

### 3.4. Association with metabolic abnormalities

Another characteristic of LPDs, which deserves attention, is its interrelation with metabolic disturbances and fever, usually in the presence of old static brain lesions. The most common metabolic derangements associated with LPDs are hyponatriemia, hypercalciemia, and hyperglycemia (Neufeld et al., 1997; Faigle et al., 2013). This relationship is explained by the reactivation of previously silent brain lesions against the background of metabolic disturbances (Neufeld et al., 1997; Singh and Strobos, 1980). We assume that increasing glutamate levels in the brain might be partially related to the reactivation triggered by metabolic disturbances.

A partial explanation for this assumption can be as follows. Fever and hyperglycemia are known to be aggravating factors of ischemic brain damage, and can also lead to acidosis (Azzimondi et al., 1995; Lindsberg and Roine, 2004). One of the critical mechanisms ensuring the survival of neurons in the penumbra is glutamate uptake by astrocytes, preventing its increase to a toxic concentration in the brain extracellular space (Swanson et al., 2004). This protective mechanism is blocked particularly by acidosis, thereby contributing to the development and enhancement of excitotoxic injury of neurons (Huang et al., 2015; Swanson et al., 1995).

Decreasing astrocytic glutamate uptake can also be observed in case of chronic hyponatremia (Fujisawa et al., 2016). Besides, glial acidosis can directly lead to release of glutamate (Beppu et al., 2014), while acute hypo-osmotic conditions stimulate glutamate release from neurons and astrocytes (Fujisawa et al., 2016).

### 3.5. Cerebrovascular correlates of excitotoxicity

Some studies have demonstrated a strong correlation between the focal increase of regional cerebral blood flow in ictal single-photon emission computed tomography (SPECT) and LPDs in EEG over relevant regions (Assal et al., 2001; Cury et al., 2004). The correlation of regional hyperperfusion to LPDs is often determined in postictal SPECT, if it is performed during the first days of seizures onset (Ali et al., 2001; Bozkurt et al., 2002). The association of LPDs with regional hyperperfusion in patients with seizures can probably be explained by the release of excitotoxins such as glutamate, which can indirectly cause persistent vasodilation (Meng et al., 1995; Deibler et al., 2008).

Finally, as mentioned above, oscillations of frequencies of greater than 8 Hz are not determined in the region of LPDs (i.e. in the intervals between LPDs complexes). It is interesting to note, that a similar phenomenon, the loss of frequencies higher than 8 Hz, has been observed in the context of primary and secondary brain ischemic injury when cerebral blood flow drops below 25 mL/100 g per minute. It is precisely this value of cerebral blood flow, which corresponds to excessive release of glutamate (Foreman and Claassen, 2012; Alkhachroum et al., 2017) and generates the penumbral zone (Liu et al., 2000; Camacho and Massieu, 2006).

## 4. Conclusion

Summarizing the arguments given above, it can be considered that neither type of brain lesion nor lesion localization is of decisive importance for LPDs generation. It is possible to conclude with high degree of probability, that the projection zone of reversible brain tissue damage becomes an exact area of the pattern manifestation. In other words, LPDs may be an EEG activity strongly characterizing the potentially reversible change in the functional activity of neurons under conditions of a relatively constant abnormally high glutamate concentration. In our hypothesis we consider glutamate excitotoxicity to be one of the key pathochemical factors for LPDs formation. The potential contribution of the GABA system is not discussed, although GABA might be related in part to the interburst interval of LPDs.

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## Author contributions statement

Dmitry Chegodaev, Olga Lvova - development of the hypothesis, search for the references, writing the manuscript; Nadezhda Pavlova, Polina Pavlova - discussion about the hypothesis, search for the references, writing the manuscript.

## Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.eplepsyres.2020.106429

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