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Mini review

Levetiracetam in brain ischemia: Clinical implications in neuroprotection and prevention of post-stroke epilepsy

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Abstract

Several new antiepileptic drugs (AEDs) have been introduced for clinical use recently. These new AEDs, like the classic AEDs, target multiple cellular sites both pre- and postsynaptically. The use of AEDs as a possible neuroprotective strategy in brain ischemia is receiving increasing attention and the antiepileptic drug levetiracetam, a 2*S*-(2-oxo-1-pyrrolidiny1) butanamide, belonging to the pyrrolidone family, could have a crucial role in regulation of epileptogenesis and neuroprotection. Recent observations suggest that levetiracetam is both safe and effective against post-stroke seizures. In this review, the potential neuroprotective role in brain ischemia and the therapeutic implications of levetiracetam in post-stroke epilepsy are discussed.

Keywords: Levetiracetam; Brain ischemia; Neuroprotection; Epileptogenesis; Post-stroke seizures

1. Introduction

Levetiracetam is a 2*S*-(2-oxo-1-pyrrolidiny1) butanamide, belonging to the pyrrolidone family, a class of drugs with a wide spectrum of actions, such as antiepileptic and neuroprotective functions [1,2]. Levetiracetam is approved as monotherapy in partial epilepsy with or without secondary generalization [3], and it maintains its efficacy and safety during long-term therapy [4]. Moreover, levetiracetam may be employed alone or in combinations with valproate, lamotrigine or phenobarbital in the treatment of idiopathic generalized epilepsies [5].

Furthermore, levetiracetam shows a particularly good balance between efficacy and tolerability, not only in the management of epilepsy but also in movement [6–9] and mood disorders [10]. Interestingly, levetiracetam might have a neuroprotective role against ischemic brain injury [11].

In the elderly, the incidence of new-onset epilepsy is higher than in any other age group and, in this frail population, the most cause of symptomatic epilepsy is represented by stroke [12]. Usually, elderly patients become seizure free with relatively low doses of antiepileptic drugs (AEDs); nevertheless, comorbidities and comedications frequently raise concerns about potentially detrimental drug interactions [12]. Among the recently-introduced AEDs, levetiracetam exhibits favourable characteristics which make it an ideal candidate as a first-choice drug for post-stroke seizures.

This review discusses the potential neuroprotective role in brain ischemia and the therapeutic implications of levetiracetam in post-stroke epilepsy.

2. Neuroprotection in brain ischemia: potential mechanisms of levetiracetam

On the basis of the similarity of the cascade of synaptic and intracellular events exhibited by epilepsy and

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vascular brain injuries, AEDs have been tested as possible neuroprotective agents in animal models of stroke [11]. Among the antiepileptic drugs, levetiracetam may have a crucial role in the regulation of epileptogenesis and neuroprotection [13]. Some particular mechanisms of action of levetiracetam might be involved in neuroprotection after vascular injury (Table 1).

Experimental observations have demonstrated that levetiracetam has a direct ability to protect against the neurotoxicity induced by chemical compounds such as kainic acid [14].

Interestingly, levetiracetam's neuroprotective properties have been investigated in the rat middle cerebral artery (MCA) occlusion model, a condition of focal cerebral ischemia [15]. In this study, application of levetiracetam reduced the infarct volume without altered body temperature, with better results than those obtained by application of a non-competitive *N*-methyl-D-aspartic acid (NMDA) antagonist [15].

The influx of calcium into cells triggers the cascade of events that brings about cell death, so it is possible that selective blockade of calcium channels may be neuroprotective. There are different classes of calcium channels. N and P/Q subtypes in particular are involved in controlling the release of neurotransmitters, while L channels regulate signalling events at a postsynaptic level. It is likely that the selective modulation of N and P/Q subtypes could be effective as a neuroprotective strategy [11]. In this sense, levetiracetam could be considered, because it regulates the influx of calcium into the cells [16–18], selectively blocking N-type [19], but not the T-type channel [20]. Moreover, there is evidence that levetiracetam reduces the flow of potassium within the cell [21]. In this way, levetiracetam modulates membrane depolarization and then interferes with the processes leading to irreversible cellular damage [21].

Furthermore, it has been demonstrated using experimental models that GABA neurotransmission is strongly depressed during brain ischemia [11]. Therefore all pre- and postsynaptic strategies supporting and increasing GABAergic levels could exerts a neuroprotective effect [22]. Although levetiracetam does not directly modulate the GABAergic system [23], it could interfere with GABA turnover [24] and with the action of GABA-A antagonists [25], as possible further mechanisms of the neuroprotective effect [26].

Negative regulation of excitatory transmission can be considered a prominent protection strategy against ischemia [27]. Modulation of ionotropic and metabotropic (group I) glutamatergic receptors has to be considered the main mechanism of neuroprotection. There is no evidence of a direct interaction between levetiracetam with glutamate receptors, but a role could be postulated in negative modulation of excitatory transmission, through a specific link to a site in the central nervous system membranes [28]. In particular, it has been demonstrated that levetiracetam binds to a synaptic vesicle protein called SV2A [29]. This is the most expressed type of a family of integral transmembrane proteins localized on all synaptic vesicles and is present in three isoforms [30]. SV2 has a crucial role in the regulation of vesicle function, although not in synaptic morphology [31]. In particular, SV2A interacts with the presynaptic protein synaptotagmin, the primary calcium sensor for regulating calcium-dependent exocytosis of synaptic vesicle [32]. It is likely that SV2A indirectly regulates neurotransmitter release. Thus, modulating SV2A function, levetiracetam could interfere with excitatory transmission, producing a neuroprotective effect [33].

Furthermore, a direct neuroprotective action of levetiracetam, by regulation of genetic transcription mechanisms has been postulated. There is evidence that the major metabolite of levetiracetam blocks histone deacetylases in HeLa cells [34]. These enzymes catalyze the hydrolysis of acetyl groups from the lysine of some proteins, such as histone tails, inducing chromatin condensation and inhibiting gene transcription [35]. Consequently, histone deacetylase inhibitors, such as levetiracetam modulate the expression of genes crucial for apoptosis. If this experimental finding could be translated into a clinical setting, the implications would be promising.

Table 1
Summary of the potential mechanisms of levetiracetam relevant to neuroprotection.

Species	Model	Mechanism	Reference
Rat	Kainic acid	Inhibition of lipid peroxidation	[14]
Rat	Hippocampal neurons in culture	Inhibition of Ca release	[16,17]
Rat	Hippocampal CA1 neurons	Reduction of potassium currents	[21]
Rat	Striatal neurons	Alterations in GABA metabolism and turnover	[24]
Rat	MCA occlusion	NA	[15]
	HeLa cells	Inhibition of histone deacetylases	[34]

MCA, middle cerebral artery; NA, not available.
Note: HeLa cell is an immortal cell line derived from cervical cancer cells taken from a patient named Henrietta Lacks.

3. Mechanisms of post-stroke epilepsy

Stroke is the most common cause of symptomatic epilepsy in older adults [36,37]. Epileptic seizures occurring more than 2 weeks after stroke, defined as late-onset post-stroke seizures, are observed in 2–4% of stroke patients [12]. There are different pathophysiological processes underlying early and late seizures after stroke, with a predominance of acute cellular biochemical disturbances in early seizures and epileptogenic gliotic scarring in late seizures [38]. The occurrence of late seizures is often delayed for months after the stroke.