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From neurogenesis to neuroprotection in the epilepsy: signalling by erythropoietin

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1. ABSTRACT

Epilepsy is a disorder characterised by recurrent seizures and molecular events, including the activation of early expression genes and the post-translational modifications of functional proteins. These events lead to changes in neurogenesis, mossy fibre sprouting, network reorganisation and neuronal death. The role of these events is currently a matter of great debate, especially as they relate to protection, repair, or further brain injury. In recent years, accumulating data have supported the idea that erythropoietin (EPO) regulates biological processes including neuroprotection and neurogenesis in several diseases, such as epilepsy. This review summarises the role of EPO in some of the molecular mechanisms involved in these events that could direct a more detailed approach for its use as a therapeutic alternative in reducing epileptic seizures.

2. INTRODUCTION

According to data from the World Health Organization (WHO), epilepsy is a common chronic brain disorder affecting approximately 50 million people worldwide. It is a complex disease characterised by the repeated occurrence of sudden and transitory episodes of motor, sensory, autonomic and psychic aura known as seizures. The anatomical, synaptic and functional consequences of seizures have been most extensively studied in the hippocampus, an epileptogenic structure that plays a central role in the generation of seizures. Epilepsy, particularly temporal lobe epilepsy (TLE), can be acquired following insults to the brain, including head injury, stroke and tumours (1, 2). Our understanding of epilepsy pathogenesis has increased considerably over the last decades from both clinical and laboratory observations. Considering epileptogenesis results in circuitry

reorganisation that can occur at either the synaptic or network level, there are multiple and diverse molecular pathways involved in epileptogenic plasticity (3, 4). Among the signalling pathways, those mediated by erythropoietin (EPO) have recently been considered neuroprotectant during the process of status epilepticus (SE). Moreover, studies in rodent models of TLE revealed that EPO significantly antagonised the development of SE (5-7).

3. EPILEPSY

Epilepsy is the second most common neurological disorder after stroke (8; 9). The incidence of epilepsy is highest in the first decade of life and after the age of 60 years (10). Chronic brain disorders have a profound impact on quality of life because most are associated with cognitive impairment and personality or behaviour disturbance. Epilepsy is one example of a prevalent and severe neurological condition (11). Traditionally, the Commission on Classification and Terminology of the International League Against Epilepsy (12, 13) has classified epilepsies based on aetiology as idiopathic epilepsy (cryptogenic) of unknown origin, epilepsy with predisposing pathology (symptomatic), or epilepsy with a suspected, but not precisely known cause (presumably symptomatic). Seizures typically arise in restricted regions of the brain and may remain confined to these areas (focal or partial) or spread to the whole cerebral hemisphere (generalised seizures).

Our understanding of epilepsy pathogenesis has increased considerably over the last decades through both clinical and laboratory observations (14-16). The mechanisms underlying seizures are complex and not uniform across the numerous seizure types that exist; however it is known that an epileptic seizure results from physiological dysfunction in the brain caused by the hypersynchronous discharge of neurons (17). The behavioural outcome of seizure events depends on the brain regions that are affected by overactivity; seizures can cause a spectrum of effects from auras accompanied by sensations such as euphoria, altered autonomic functions, loss of consciousness and motor changes, including whole body convulsions (8). These characteristics are clearly exemplified in temporal lobe epilepsy (TLE), the most frequent type of human epilepsy (18).

3.1. Mesial Temporal Lobe Epilepsy

Temporal lobe epilepsy (TLE) is the most common form of human epilepsy; it can evolve after an initial insult, such as complex febrile seizures, stroke, brain infections, head trauma, ischemic lesions, brain tumours or status epilepticus (19, 20). After damage, the majority of these patients suffer from symptomatic focal epilepsies ("simple partial" seizure), which arise in a restricted part of the limbic system. Moreover, the seizures can also spread to other regions of the temporal lobe, such as the amygdala ("complex partial"), and may subsequently spread to the whole brain ("secondarily generalised") (16). In the majority of TLE cases, the initial epileptogenic focus involves the hippocampal formation, which displays major neuropathological features described with the term "hippocampal sclerosis" (HS) (21-23). This features the selective loss of neurons that are typically asymmetric between the hippocampus regions. For example, granule cells in the dentate gyrus are remarkably resistant to neuronal damage caused by most insults, including seizures (24), while pyramidal neurons are extremely vulnerable, particularly in the CA1-region (25). Additional features can include axonal sprouting and the dispersion of neurons in different layers and gliosis in the hippocampus (3, 26).

Abnormal hippocampal morphology and aberrant neuronal connections are characteristic in both temporal lobe epilepsy and in pilocarpine- and kainic acid- injected animal models (24, 27). Among the hypothetical mechanisms responsible for TLE are neuronal cell loss and gliosis in the CA1 and hilus and the formation of new recurrent excitatory circuits after mossy fibre sprouting. Other alterations include the dispersion of granule cells, the synaptic reorganisation of the mossy fibres and the degeneration of hilar interneurons with subsequent diminished inhibitory synaptic transmission onto distal dendrites of dentate granular cells as well as neurogenesis (28, 29). These long-lasting plastic changes in the brain are key factors in the conversion of a non-epileptic to an epileptic brain (30, 31). Therefore, the anatomical, synaptic and functional consequences of seizures have been most extensively studied in the hippocampus because that structure plays a central role in epileptogenesis (32).

3.2. Epileptogenesis and the hippocampus

The term epileptogenesis is often associated with the development of symptomatic, acquired epilepsy that presents with an identifiable structural lesion in the brain, and it is used to refer to a latency period between the occurrence of the insult and the appearance of the first spontaneous seizure (33). Epileptogenesis is characterised by a dynamic process that progressively alters neuronal excitability, establishes critical interconnections, and requires intricate structural changes, which include neurodegeneration, neurogenesis, gliosis, axonal damage or sprouting, circuitry rearrangements and individual synapses, the recruitment of inflammatory cells into brain tissue, and the reorganisation of the extracellular matrix (Figure 1). All of these structural changes produce modifications in both the intra- and extra-cellular signals of individual neuronal cells. Both the dynamic processes and the structural changes occur before the first spontaneous seizure (34, 35).

If brain damage or aberrant plasticity following an insult is the major cause of subsequent epilepsy, the administration of a neuroprotective or neuromodulatory drug immediately after insult might be effective at preventing epilepsy development. Particularly, the hippocampal circuitry is endowed with plastic properties having important implications for epileptogenesis (31, 32).

4. NEUROGENESIS IN EPILEPSY

The formation of the central nervous system (CNS) happens through successive phases during the embryonic and early postnatal periods with a vast majority

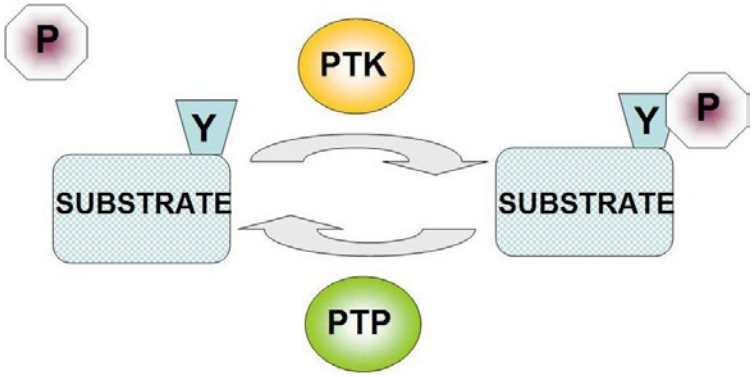

Figure 1. A schematic of the complexity of the cellular and molecular mechanisms in Epilepsy

of cells; however, it is well accepted that new neurons are continuously added in specific regions of the mammalian brain throughout adulthood (36, 37). Adult neurogenesis is involved in physiological conditions such as learning and memory (38), and the impact of new neurons on the adult neuronal circuitry is determined by their physiological properties and synaptic connectivity (39). Neurogenesis in the hippocampus has been correlated with learning and memory; moreover, it is the only intrinsic response of the adult brain to injuries such as addiction, depression, epilepsy and schizophrenia (40, 41). In particular, the hippocampus is capable not only of re-organisation when intact but also when it is damaged. Among these changes, perhaps the most basic of all structural changes is the addition of new neurons (neurogenesis). Additionally, dynamic modifications continually form in dendritic extension and retraction as well as in synapse formation and elimination (42-44).

Aberrant neurogenesis and neuronal cells loss is characteristic of the cellular response to prolonged seizure activity (45). These alterations can contribute to the detrimental long-term consequences of status epilepticus (Figure 1) (46). A dramatic increase in the production of new neurons was observed in the granule cell layer of the DG following pilocarpine-induced SE (47) or kindling stimulations (48). A proliferative surge occurs in neural stem cells (NSCs) of the subgranular zone shortly after SE, leading to the increased production of new neurons after a seizure episode (49, 50) mediated by excitatory stimuli (51). However, gamma-Aminobutyric acid (GABA) has a crucial role in regulating various steps of adult neurogenesis, including the proliferation of neural progenitors and the synaptic integration of new-born neurons (52). Additionally, increased levels of neuropeptide Y (NPY) enhance proliferation (53) and also modulate neuron-restrictive silencing factor (NRSF) activity, increasing neurogenesis after acute seizures (54). The involvement of neurotrophic factors and other proteins increase the proliferation of NSCs in the hippocampus. These factors include nerve growth factor (NGF), brain-derived neurotrophic factor (BDNF), fibroblast growth factor-2 (FGF-2), vascular endothelial growth factor (VEGF) and Sonic hedgehog (Shh) (55, 56, 53).

Several studies have determined an increase in neurogenesis after acute seizures in rats (54, 45, 46), however the extent of neurogenesis declines radically in the chronic phase of epilepsy when significant numbers of spontaneous seizures manifest (57); both a gradual decrease at 1 week and a virtual loss of neurogenesis by 4–6 weeks after the initial seizure episode have been reported (58). It has also been reported that there were no changes in neurogenesis in the hippocampus after electrically evoked SE, while in lithium-pilocarpine models, epilepsy modestly increases neurogenesis 2 months post-SE (59, 60). The mechanisms underlying decreased neurogenesis in chronic epilepsy are unknown; it has been proposed that an unfavourable NSC milieu can be gleaned from decreased levels of some neurotrophic factors in chronic epilepsy (57, 56). Thus, it has been proposed that diminished hippocampal neurogenesis might contribute to the persistence of spontaneous seizures, learning and memory impairments and depression that are prevalent in epilepsy (61).

4.1. Involvement of EPO in neurogenesis

EPO is a 30.4.-kDa glycoprotein consisting of 165 amino acids and has a disulphide bond between the cysteines at positions 7 and 161. This bond is functionally important because it acts as a tether and ensures the molecular configuration required to maintain the bond with its specific membrane receptor (EPOR), thereby regulating erythropoiesis (62, 63) with a potential neuroprotective effect (64).

The production and secretion of EPO and the expression of its receptor (EPOR) in several tissues are regulated by tissue oxygenation levels and exert pleiotropic activities (65). In the brain, the basal expression of EPO is found in both neurons and astrocytes, while both post-ischemia and post-epilepsy EPO expression is localised in endothelial cells, microglia/macrophage-like cells, (66) and astrocytes (67, 68). The signalling mediated by EPO/EPOR is required for normal brain development (69) that stimulates neuronal progenitor cell production from pluripotent cells, increasing neurogenesis as well as neural-progenitors migration in both the subventricular zone and the dentate gyrus into the cortex, striatum and hippocampus of neonatal rats (70, 71). Mark *et al*. (2008) showed that EPO stimulates the Akt signalling pathway and that the effects of EPO are related to axonal growth and neurite

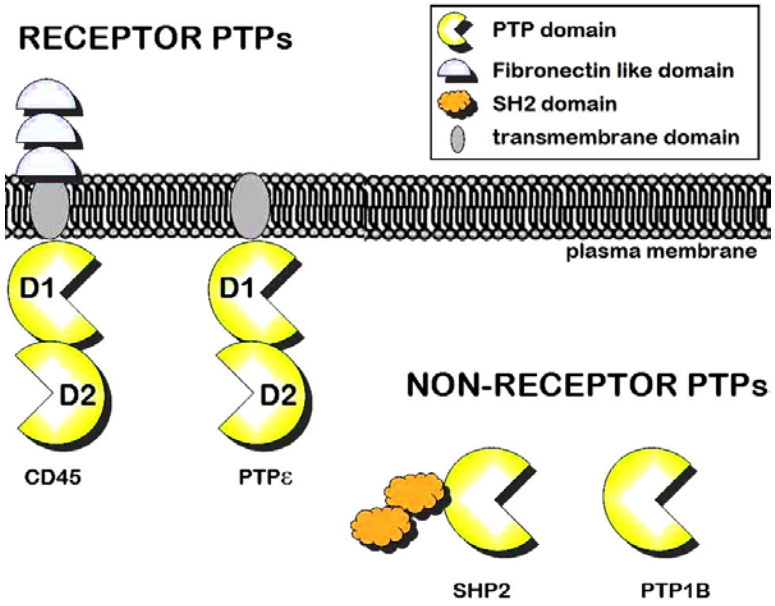

Figure 2. Molecular events both neuroprotection and neurogenesis are mediated by erythropoietin, in brain damage

outgrowth in hippocampal neurons. Pro-neuronal transcription factors, including Mash1 and Neurogenin1 (Ngn1), promote neural-progenitor differentiation into neurons, demonstrating that Mash1 and Ngn1 regulate EPO-mediated neuronal differentiation (72). In addition, intracerebroventricular EPO infusion significantly enhanced the survival of NSCs but not neuronal differentiation or migration after kainic acid induced-SE. However, NSC transplantation increased the number of NPY- and glutamic acid decarboxylase 67-positive interneurons (73). In turn, the delayed administration of EPO after a damaging event also concurrently promotes oligodendrogenesis with increased neurogenesis, which is likely to contribute to the observed improvement in neurological functional outcomes (74).

4.1.1. Additional pathways associated to EPO

Wnt plays a role in a variety of cellular functions that involve embryonic cell proliferation, differentiation, survival and death (75, 76). Wnt signalling can prevent cell injury through a variety of mechanisms; it prevents apoptosis through β-catenin/Tcf transcription-mediated pathways (77), and it can also protect cells against c-myc-induced apoptosis through cyclooxygenase-2 and (78) β-amyloid toxicity, which may require the modulation of glycogen synthase kinase-3 β (GSK-3β) and β-catenin (79). Interestingly, EPO maintains the expression of Wnt1 during elevated glucose exposure in diabetic patients. More importantly, the blockade of Wnt1 with a Wnt1 antibody can neutralise the protective capacity of EPO, illustrating that Wnt1 is a critical component in the cytoprotection by EPO (79). The Wnt pathway inhibits GSK-3β activity that may increase cell survival during oxidative stress, and as a result, GSK-3β is considered to be a therapeutic target for some neurodegenerative disorders (80). It has been shown that EPO phosphorylates and inhibits GSK-3β activity (Figure 2) (81).

5. NEUROPROTECTION AND EPILEPSY

Hippocampal neuronal death, particularly in CA1-pyramidal cells, is common in the injuries caused by cerebral ischemia (82), epilepsy (7, 67, 83) and subsequent seizures by acute hypoxia (84). Recent studies clarify the domain of anti-epileptogenic and neuroprotective strategies for protecting and repairing neurons in post-SE conditions (31, 85). The developments of strategies for the use of candidate neuroprotectants as a therapeutic approach to prevent epileptogenesis are the most appealing; an emerging molecule for this treatment is likely EPO.

5.1. Neuroprotective effect of EPO

As previously mentioned, the role of EPO in neurogenesis appears to be its ability to prevent metabolic damage, vascular and neuronal degeneration and inflammatory responses through different signalling pathways (Figure 2) (86, 87). It has been proposed that this molecule is a critical mediator of protection and the plastic phenomena generated by a damaging event (88). The neuroprotective effect of EPO results in the beneficial modification of cognitive functions in humans and in animals (89, 90). Both EPO and EPOR are expressed in the hippocampus of rodents and primates (91, 92) and have been shown to be involved in synaptic plasticity and memory improvement (89, 93). Evidence in hypoxia-ischemia and trauma models in both adult and neonatal rodents have shown that the effect of insulin (94), hypoglycaemia (95) and intense neuronal activity leads to the synthesis of EPO in neurons and astrocytes (96, 97). In turn, EPO administered exogenously has a neuroprotective role through regulating anti-apoptotic and anti-inflammatory mechanisms (98, 99), and secondly, EPO administration itself leads to gene transcription and the production of both EPO (100) and EPOR (101).

A mouse toxicity model induced by kainate administration (20 mg/kg) generally results in seizures (102, 103) and death 18 minutes after SE; the mice receiving EPO (5000 UI/kg) had delayed onset of status epilepticus and reduced motor involvement (104). Moreover, in the developing rat brain after pilocarpine-induced SE, EPO administration (4000 UI/mL) may preserve the number of neurons and decrease apoptosis. The mode of action of EPO on seizure activity is presumably different from that of conventional anti-epileptic drugs (105). Furthermore, EPO administration prevented BBB leakage, neuronal death, microglia activation and inhibited the generation of ectopic granule cells (106). EPO administration coupled with astroglial induction of EPO following SE is protective (6). EPO infusion can enhance the survival of grafted NSCs, with NPY-positive cells in the dentate gyrus ameliorating spontaneous recurrent seizures after a KA lesion (73).

5.1.1. EPO Signalling pathways.

The protective role of EPO in neurons is established by binding to its receptor. The signalling pathway involves the activation of Janus tyrosine kinase 2 (JAK2), which propagates the signal through signal transducer and activator of transcription (STAT), mitogen-activated protein kinase (MAPK) and phosphatidylinositol-3-kinase (PI3K/Akt) (107). The activity of these pathways contributes to different cellular functions and is an essential regulator of proliferation and cell survival (108). Akt can phosphorylate different members of the pro-apoptotic Bcl-2 family, such as Bad (109) and Bim (110); once phosphorylated bind to the chaperone 14-3-3 in the cytoplasm, thereby inactivating pro-apoptotic functions (109, 110). The inactivation of pro-apoptotic factors p53 and p73 by Akt has also been described (111). It has been shown that EPO activates the PI3K/Akt pathway in a variety of experimental models of injury (112, 113), such as epilepsy (Figure 2) (114). These effects can involve transcription factor regulation, maintenance of $\Delta\Psi m$, the prevention of cytochrome c release and the blockade of caspase activity modulating calcium influx in KA-induced epilepsy (62, 114, 115).

The classical function by STAT signalling pathways is through both pro-apoptotic and anti-apoptotic signals, depending on the conditions of cell stimulation (116). However, it has been shown that STAT5 is predominantly a pro-survival signal activated by several cytokines and growth factors, such as EPO and interleukins (117,92). STAT5 appears to be expressed in the hippocampus and cortex of both the embryonic and adult rat brain (118). The end effectors of STAT5 signalling include Bcl-xL and XIAP, both proteins with anti-apoptotic effects (Figure 2) (119, 120).

EPO significantly activates ERK 1/2 in primary cerebral vascular cells during oxidative stress (121). Additionally, ERK1/2 signalling pathways mediate EPO-modulated calcium influx in KA-induced epilepsy, suggesting that EPO may require these cellular pathways to confer cytoprotection (Figure 2) (114).

Another direct effect on the apoptotic pathway by EPO involves the modulation of caspase activity, which may offer several avenues for protection against cell injury, including the prevention of specific caspase 1- and caspase 3-like activities, inactivation by the phosphorylation of caspase-9, or the negative regulation of SAPK/JNK (115, 122-124). EPO also can block genomic DNA degradation through the inhibition of cytochrome c release and the subsequent inhibition of caspase 3-like activity (115). Moreover, the regulation of caspase 3-like activity by EPO has recently been linked to a unique mechanism that blocks the proteolytic degradation of phosphorylated forkhead transcription factors (125, 126). It prevents cellular apoptosis through parallel pathways, preventing the induction of Apaf-1 and caspase 9 as well as preserving mitochondrial membrane potential in conjunction with enhanced Bcl-xL expression (115). Furthermore, EPO preconditioning, except direct neuroprotection in the acute phase of seizure-induced cell injury, can suppress apoptotic neuronal cell death by regulating the expression of Bim and Bid (7).

5.2. EPO Variants

Several strategies have been proposed in efforts to separate the neuroprotective effects from the erythropoietic effects of EPO. However, carbamylated erythropoietin (CEPO), a non-erythropoietic derivative of EPO that does not bind to the classical EPOR, is neuroprotective in acute stroke but does not elevate hematocrit levels (104). CEPO could activate the Shh signalling pathway and mediate its effect on neural progenitor cells (127). Repeated doses of EPO treatment immediately after hypoxic-ischemia contribute to neurovascular remodelling by promoting tissue protection, revascularisation and neurogenesis in the neonatal injured brain and improve neurobehavioral outcomes (70). Wang *et al*. (128) present a head-to-head comparison of the protective effect of EPO and CEPO in a rat model of stroke following embolic middle cerebral artery occlusion (MCAO). EPO, at dose of 500–5000 IU/kg, or CEPO, at a dose of 50 mg/kg, significantly reduced infarct volume and improved functional outcome when administered 6, 24 and 48 h after embolic MCAO. Lower doses of EPO (500 IU/kg), with less effect on the haematocrit, also resulted in significantly decreased neuroprotection. In contrast to this observation, CEPO (50 mg/kg) offered the same neuroprotection as 5000 IU/kg of rhEPO but without any haematological side effects. Moreover, asialo-erythropoietin exhibited neuroprotection in rodent models of focal ischemia and hypoxia in the brain and in spinal cord compression when administered intravenously at the time of challenge or 24 h before (129). Therefore, because of its rapid clearance from the circulation, asialo-erythropoietin administration in rodents is able to uncouple the stimulation of erythropoiesis from the neuroprotective effects associated with EPO (130, 131).

The beneficial effects of EPO-variants using ischemia models have been successful but need to be expanded to therapeutic uses in other disorders, such as epilepsy, to help counteract epileptic seizures.

6. CONCLUSION

Erythropoietin has proven to be a molecule that limits the extent of injury through the maintenance of neurogenesis and the survival of neurons undergoing damage produced by diverse pathologies, such as epilepsy. A therapeutic approach using EPO could help to reduce epileptic seizures because both molecular and cellular events are involved in the course of epileptogenesis. Therefore, it is of great importance to know the pathways activated by EPO to further a successful clinical application to reduce epileptic seizures.

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