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Regeneration in the nervous system with erythropoietin

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Abstract

Globally, greater than 30 million individuals are afflicted with disorders of the nervous system accompanied by tens of thousands of new cases annually with limited, if any, treatment options. Erythropoietin (EPO) offers an exciting and novel therapeutic strategy to address both acute and chronic neurodegenerative disorders. EPO governs a number of critical protective and regenerative mechanisms that can impact apoptotic and autophagic programmed cell death pathways through protein kinase B (Akt), sirtuins, mammalian forkhead transcription factors, and wingless signaling. Translation of the cytoprotective pathways of EPO into clinically effective treatments for some neurodegenerative disorders has been promising, but additional work is necessary. In particular, development of new treatments with erythropoiesis-stimulating agents such as EPO brings several important challenges that involve detrimental vascular outcomes and tumorigenesis. Future work that can effectively and safely harness the complexity of the signaling pathways of EPO will be vital for the fruitful treatment of disorders of the nervous system.

Keywords

Akt; AMPK; apoptosis; autophagy; erythropoietin; forkhead; FoxO; mTOR; oxidative stress; rapamycin; sirtuin; SIRT1; stem cells; trauma; WISP1; Wnt; Review

2. INTRODUCTION

In the large developing nations that include India and China, the number of elderly individuals will increase from current levels of approximately 5 percent to almost 10 percent over the next several decades. Aging of the population also is occurring at a significant rate in developed nations around the globe. In these nations, the number of individuals over the age of 65 has doubled during the prior 50 years (1). Life expectancy is increasing in these developed countries and is accompanied by a one percent decrease in the age-adjusted death rate from the years 2000 through 2011(2). Although improvements of healthcare and stable environments are important factors for the increased longevity of the world's population, a rise in chronic pathologic disorders has paralleled the aging of the world's population. According to the World Health Organization, more than 60 percent of the 57 million global deaths result from noncommunicable diseases (NCDs) and almost 80 percent of these NCDs occur in low and middle-income countries (3). In particular, a rise in the incidence of neurodegenerative disorders is expected to ensue (4, 5). Acute and chronic

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neurodegenerative disorders lead to disability and death in more than 30 million individuals worldwide (6).

Chronic neurodegenerative disorders such as Alzheimer's disease (AD) can impact a large proportion of the global population (7). Although familial cases of AD represent less than 2 percent of all presentations (8), usually occur prior to age 55 (9), and represent an autosomal dominant form of a mutated amyloid precursor protein (APP) gene as well as mutations in the presenilin 1 or 2 genes (10), 10 percent of the global population over the age of 65 are affected with sporadic AD. For disorders such as Parkinson's disease (PD), also a chronic progressive neurodegenerative disease (11, 12), approximately 50,000 new cases present in the United States alone each year. It is estimated that 1 to 4 percent of individuals over 60 suffer from PD in the world and this number of affected individuals may double by the year 2030.

Acute neurodegenerative disorders also place a severe burden on the world's population (13, 14). Cerebrovascular disease leads to multiple complications that affect both the livelihood and minimal daily function of an individual (15, 16). Approximately 15 million individuals suffer from a stroke every year, one of the five leading causes of death (17). NCDs such as cardiovascular disease and diabetes can contribute to acute neurodegenerative disease that include stroke (18, 19). In the United States, almost 800,000 strokes occur per year at an annual cost of 75 billion US dollars (13). Traumatic brain injury (TBI) also leads to neurological disability and death throughout the world (20, 21). TBI can have a two-fold effect to result in acute injury to the nervous system as well as subsequent chronic impairment (22–24). In the United States, approximately 50,000 individuals die every year as a result of TBI and more than 100,000 individuals suffer with chronic disability (25). If severe trauma occurs, almost one half of these individuals will eventually die.

3. THE GROWTH FACTOR AND CYTOKINE ERYTHROPOIETIN

3.1. Background of erythropoietin

Both acute and chronic neurodegenerative disorders comprise a broad array of pathologies in the nervous system. As a result, numerous therapeutic strategies are under development for neurodegenerative disease. These include therapies directed against oxidative stress (20, 24, 26–34), exposure to metal toxicity (35–39), loss of sirtuin activity (4, 7, 40–48), poly(ADP-ribose) polymerase-1 (PARP-1) over-activation (49–59), decreased metabotropic glutamate activity (60–72), cellular metabolic dysfunction (19, 28, 73–78), defects in gamma-aminobutyric acid (GABA) signaling (79–83), transcription factor activation (4, 47, 80, 84–99), Src homology-2 (SH2) domain phosphorylation (100–107), components of the mechanistic target of rapamycin (mTOR) pathway (7, 16, 108–120), and growth factors (119, 121–125).

In the armamentarium of new agents under development, the cytokine and growth factor erythropoietin (EPO) offers exciting and new prospects for the treatment of neurodegenerative disorders. The *EPO* gene resides on chromosome 7, represents a single copy in a 5.4. kb region of the genomic DNA, and encodes for a polypeptide chain that has initially 193 amino acids (126). Once generated as a protein, EPO is then processed and

cleaved of a 27 amino acid hydrophobic secretory leader at the amino-terminal to result in a 166 amino acid peptide (127). A mature protein is subsequently formed with the removal of a carboxy-terminal arginine^{166} in the mature human and recombinant human EPO (rhEPO) to generate a circulatory EPO protein of 165 amino acids with a molecular weight of 30.4. kDa (128–131) (Table 1).

The concept of circulatory and potentially protective proteins in the body actually predated the discovery of EPO. Ernest Sterling in 1905 introduced the term "hormones", a term with Greek origins meaning to "excite" or "arouse", to describe the action of agents that are blood borne to target distant organs of the body (132). Prior to this discussion, Arnold Adolphe Berthold described messenger signals that could communicate among the different bodily organs (133). In addition, Claude Bernard spoke about the internal secretion of chemicals in the body with the release of glucose from glycogen in the liver (129, 134).

3.2. Expression of erythropoietin

EPO and its receptor (EPOR) are expressed in numerous tissues and initially it was presumed that EPO functioned only as a circulatory agent in the body. In 1906, Carnot and Deflandre performed studies to show that following a bleeding stimulus in rabbits, immature red blood cells in these animals would be produced (135). Carnot and Deflandre termed this agent as “hemopoietine”. This work was repeated and confirmed by other investigators to observe reticulocytosis in bled animals (136–138).

The agent responsible for this reticulocytosis was later termed EPO. Human EPO protein was eventually purified. The gene for *EPO* was cloned and allowed for the development of recombinant EPO for clinical use (139, 140). At present, erythropoiesis-stimulating agents (ESAs), which include EPO, are approved for the treatment of anemia that results from chronic kidney failure, human immunodeficiency virus, chemotherapy, and to reduce blood transfusions for surgery (141, 142). The primary site for the production and secretion of EPO are the kidney peritubular interstitial cells (143). EPO also is present in other organs that include the brain, uterus, and liver (143–147).

During development, production of EPO and EPOR are modified (129). EPO production in gestation is increased, but later EPO is suppressed following birth to be regulated by the tissue oxygen supply. Although elevated expression of the EPOR is present in early embryonic neuronal tissues, EPOR expression is significantly reduced following the maturation of the brain. EPO secretion in the brain is more sustained than in peripheral organs such as the kidney, suggesting that EPO production may originate in the brain and possibly crosses the blood-brain barrier to reach the blood and peripheral organs. Primary neurons and neuronal cell lines also are able to retain the capacity to express EPO in an oxygen-dependent manner (126, 141).

3.3. Structure and activity of erythropoietin

The integrity of EPO is dependent upon the structure and the maintenance of the oligosaccharide side chains (147, 148) (Table 1). EPO contains four glycosylated chains that include three *N*-linked and one *O*-linked acidic oligosaccharide side chains (149). The *N*-

linked glycosylation sites occur at aspartyl[24], aspartyl[38], and aspartyl[83]. The *O*-linked glycosylation site occurs at serine[126]. The *N*- and *O*-linked chains may be required for the production and secretion of the mature EPO (148). The carbohydrates are important for the clearance of EPO, since EPO molecules with high sialic acid content can be easily cleared by the body through the liver (150).

The molecular structure of EPO also determines the biological activity of this protein. The oligosaccharides in EPO have been reported to provide protection from free radical activity (151) and the carbohydrate chains of EPO stabilize the protein (152). The glycosylated chains also protect EPO from free radical oxygen degradation (149). In addition, reduction of the two disulfide bonds formed between cysteine[7] and cysteine[160] and between cysteine[29] and cysteine[33] leads to the loss of activity of EPO. Alkylation of the sulfhydryl groups leads to irreversible loss of the activity of EPO. Re-oxidization of EPO after reduction by guanidine restores almost 85 percent of the biological activity of EPO (153).

3.4. Production of erythropoietin

Almost seven decades prior, EPO was correlated to depressed oxygen levels. In parabiotic rats when only one partner was exposed to hypoxia, EPO was demonstrated to increase hemoglobin levels (154). Prior to such studies, EPO levels were believed to be correlated with decreased red blood cell counts. However, EPO expression is now known to be regulated by changes in oxygen tension and not by the concentration of red blood cells (144, 155, 156) (Table 1). Hypoxia-inducible factor 1 (HIF-1) modulates the expression of EPO and the EPO receptor (EPOR) to increase the production of EPO as required (126, 144, 157, 158). Independently, HIF-1 is an agent that can promote cellular protection against injury (159–161). Once HIF-1 is activated, gene transcription of EPO and EPOR occurs and is controlled through the transcription enhancer region in the 3'-flanking region of the EPO gene that binds to HIF-1 (126, 129).

EPO also is regulated through pathways that may not rely upon exposure to hypoxia (132). EPO in the amniotic fluid of patients with diabetes can be elevated (162). It is unclear if this suggests an attempt to repair tissue at risk for injury by EPO, but EPO blood levels are elevated and associated with greater disability during brain maturation exposed to a toxic environment (163). Insulin can stimulate EPO production in specific cells that include astrocytes (164). During chronic hyperglycemia in adults, EPO levels can become depressed (165). Agents that decrease inflammation in cerebral microglia have been demonstrated to lead to the release of EPO (166). Malaria can result in significant serum levels of EPO (167) and EPO serum concentrations are raised during xenon anesthesia in cardiac surgery (168). Depletion of selenium, an anti-oxidant, can lead to increased EPO expression (169). Cadmium exposure, raised intracellular calcium, and neuronal depolarizations can affect the expression of EPO (145, 149, 170). In addition, cytokines, including insulin-like growth factor (IGF), tumor necrosis factor-α (TNF-α) (171), interleukin-1β (IL-1β), and interleukin-6 (IL-6) can increase EPO and the EPOR expression (126, 147, 172).

4. SIGNALING PATHWAYS OF ERYTHROPOIETIN

4.1. Erythropoietin and protein kinase B (Akt)

EPO relies upon multiple signaling pathways that can lead to tissue repair and cellular protection. Phosphoinositide 3-kinase (PI 3-K) and protein kinase B (Akt) are principal pathways that offer cellular protection through EPO (Table 1). PI 3-K phosphorylates membrane lipids and regulates the transition of Akt from the cytosol to the plasma membrane (173). Akt is phosphorylated on the serine^{473} and threonine^{308} residues by phosphoinositide dependent kinase (PDK) PDK1 and PDK2 (103, 174, 175). Independently, Akt can lead to the protection of of cells in the nervous system during estrogen signaling (176), activation of pro-apoptotic proteins (27, 47, 62, 84, 86, 177–179), spinal muscular atrophy (180), protein phosphatase activity (181), β-amyloid (Aβ) toxicity (99, 182–193), oxygen-glucose deprivation (194–198), hypoxia (109, 199–202), and in models of diabetes mellitus (203–208).

EPO can phosphorylate Akt at serine^{473} to activate Akt (141, 209–213). Through Akt, EPO can affect both the function and survival of cells. In endothelial cells, EPO improves the vasculogenic potential of peripheral blood mononuclear cells and promotes adhesiveness of the cells through Akt activation (214). In regards to increased survival, EPO activates Akt to prevent oxidative stress and injury from free radicals (194, 199, 203, 209–211, 215, 216), prevent Aβ toxicity in microglia and neurons (186, 217–219), block vascular demise and reduce inflammation (194, 199, 203, 204, 216, 220–226), and foster neuronal and non-neuronal cell survival (196, 210, 215, 227–229).

4.2. Erythropoietin, forkhead transcription factors, sirtuins, and Wnt signaling

In addition to Akt, EPO controls the signaling pathways of mammalian forkhead transcription factors of the O class (FOXO), the silent mating type information regulation 2 homolog 1 (*S. cerevisiae*) (SIRT1), and Wnt proteins, derived from the *Drosophila Wingless* (*Wg*) and the mouse *Int-1* genes. Mammalian FOXO proteins include FOXO1, FOXO3, FOXO4, and FOXO6 (230). For the nomenclature of these proteins, all letters are capitalized for human Fox proteins. However, in the mouse, only the initial letter is listed as uppercase. In addition, for all other chordates the initial and subclass letters are in uppercase (93). Since they are transcription factors, FoxO proteins bind to DNA (231, 232) to affect the transcription of proteins that usually are “pro-apoptotic” (233). Multiple processes control the activity of FoxO proteins (234). These can include the regulation of the translocation of FoxO proteins to the nucleus. For example, Akt activation leads to phosphorylation of FoxO proteins that will bind FoxO proteins to 14-3-3 proteins, prevent nuclear translocation, and block the transcription of target genes that promote apoptosis (47, 169, 194, 235). In addition, other post-translation protein changes in FoxO proteins include acetylation (47, 95, 236), ubiquitylation (54, 97, 206, 232), and phosphorylation (47, 86, 99, 178, 194, 204, 207, 236–240). Acetylation of FoxO proteins can increase the Akt mediated phosphorylation of these proteins (241) and inhibit ubiquitination (93). In neurons, FoxO3a activation and p27 (kip1) transcription can result in apoptosis (242). In microglial cells and neurons, knockdown of FoxO3a and blockade of FoxO3a translocation to the nucleus leads to the increased survival during oxidative stress (47, 243). Phosphorylation of FoxO3a and

the nuclear export of FoxO3a protects neurons (244) and endothelial cells in models of experimental diabetes mellitus (204, 206, 207, 221). During stroke in animal models, FoxO3a interaction with cell cycle induction proteins may play a role in neuronal apoptotic cell death (95).

The sirtuin SIRT1 has a significant role in the control of FoxO proteins (4). As a histone deacetylase, SIRT1 reversibly deacetylates FoxO proteins (41) and can maintain cellular and tissue function during periods of starvation through pathways involving autophagy (245). Through the deacetylation of FoxOs, SIRT1 leads to increased cortical bone formation with osteoblast progenitors by blocking FoxO protein binding to β-catenin that would inhibit Wnt signaling (246). SIRT1 and FoxO proteins may work synergistically to protect cells. Increased FoxO3a and SIRT1 activity with a reduction in autophagy limits oxidative stress in human bronchial epithelial cells exposed to cigarette smoke condensates (247). Loss of the forkhead transcription factors FoxO1 and FoxO3 in combination with decreased SIRT1 activity during oxidative stress leads to a reduction in autophagy and subsequent chondrocyte cell death, suggesting that SIRT1 with FoxO proteins may be required for cellular protection during oxidative stress (248).

Several studies also suggest that inhibition of FoxO protein activity that requires SIRT1 activity can increase cell survival. SIRT1 can increase lifespan in higher organisms and offer protection against oxidative stress in neuronal cells (249). SIRT1 activity can foster cell survival in the nervous system through the blockade of FoxO protein activity (41, 250–253). During this protective process, promotion of SIRT1 nuclear translocation increases neuronal survival (47). If SIRT1 activity is lost, FoxO1 expression during high glucose exposure can lead to endothelial cell dysfunction (254). Of note, the amount of SIRT1 activity can be a critical modulator of cell survival. SIRT1, and in general sirtuins, play a significant role during vascular repair (207, 255–257) and cardiovascular disease (4, 258). Exercise training in rodents can limit age-related impairments though the increase in anti-oxidant pathways and the up-regulation of SIRT1 activity and FoxO3a expression (259). Yet, it appears that anti-oxidant activity such as through catalase expression and FoxO protein dependent pathways requires SIRT1 activity that increases less than 7.5.-fold (260). Levels of SIRT1 activity that exceed 12.5.-fold can result in apoptosis and cardiac dysfunction (260).

SIRT1 activity can be regulated by several pathways. FoxO proteins can control SIRT1 transcription and increase SIRT1 expression (261). Furthermore, apoptotic pathways associated with p38 (262) and c-Jun N-terminal kinase −1 (JNK1) (263) can reduce SIRT1 activity and increase caspase activity that can lead to the degradation of SIRT1 (264). Pathways that involve Wnt signaling can block the degradation of SIRT1, maintain its activity, and prevent caspase activation (27, 47, 265, 266). Wnt proteins are cysteine-rich glycosylated proteins that are proliferative in nature and oversee vascular cell development (267–269), stem cell development (122, 246, 270–273), cellular turnover (274), immune function (251, 275–277), tumor cell growth (236, 271, 278–281), and neuronal survival (156, 275, 282–284). In the brain, loss of Wnt signaling may be tied to cognitive decline (282), spinal cord injury (285, 286), oxidative stress injury (47, 197), long-term memory impairment (287), immune cell loss (243, 277, 288–290), neurodegenerative disorders (284, 291, 292), depression (293), and cerebral ischemia (294–296). Wnt signaling protects

against programmed cell death (183, 297, 298) and uses β-catenin for the phosphorylation and inhibition of FoxO proteins such as FoxO3a during oxidative stress (239). In neurons, Wnt signaling activates Akt (183, 197, 299, 300), limits the deacytelation of FoxO3a (47), and maintains FoxO3a in the cytoplasm to prevent the loss of mitochondrial membrane permeability, cytochrome c release, Bad phosphorylation, and activation of caspases (243). Wnt1 inducible signaling pathway protein 1 (WISP1/CCN4) is a target of Wnt1 signaling that regulates programmed cell death, extracellular matrix production, tumorigenesis, cellular migration, fibrosis, and mitosis (268, 274, 278, 301–303). Similar to Wnt1 signaling, WISP1 protects neurons through the phosphorylation of FoxO3a, by sequestering FoxO3a in the cytoplasm with protein 14-3-3, and by limiting deacytelation of FoxO3a (47). WISP1 also promotes SIRT1 activity and trafficking to the cell nucleus (47). Conversely, FoxO proteins can block Wnt signaling. FoxO3a can bind to β-catenin and reduce the expression of β-catenin target genes (304). FoxO proteins also may antagonize Wnt signaling pathways during oxidative stress and aging to block the proliferation of osteoblast precursors (305).

For FoxO proteins, EPO controls the nuclear translocation and the post-translational processing of FoxOs to promote cellular survival (29) (Table 1). Through the activation of Akt, EPO can phosphorylate and inactivate FoxO proteins (306) such as FoxO3a (194, 307–309). EPO can promote the binding of FoxO3a to 14-3-3 protein to sequester FoxO proteins in the cytoplasm of cells and prevent nuclear translocation and transcription of “pro-apoptotic” proteins (169, 194, 310). EPO promotes eythroid progenitor cell development that requires the modulation of FoxO3a activity (147, 169, 311). In addition to FoxO3a phosphorylation, EPO subsequently down-regulates the protein p27 (kip1) involved in inhibition of cell cycle regulation (237). EPO can protect brain endothelial cells during periods of oxygen-glucose deprivation by phosphorylating FoxO3a, inhibiting the activity of the protein, and blocking translocation to the nucleus (221, 312). In models of cerebral ischemia, EPO limits activities of FoxO1 in addition to other pathways to reduce ischemic stroke size (313).

Closely linked with the neuroprotective capacity of EPO is SIRT1 and Wnt signaling (Table 1). In adipocytes, EPO increases metabolic activity and maintains adipose energy homeostasis to protect against the complications of metabolic disorders through the combined activation of peroxisome proliferator-activated receptor-alpha (PPARα) and SIRT1 (314). In regards to cellular differentiation, EPO employs SIRT1 to modulate skeletal myogenic differentiation (315). In endothelial cells of the brain during oxygen-glucose exposure, EPO promotes the subcellular trafficking of SIRT1 to the nucleus which is necessary for EPO to foster vascular protection and to prevent mitochondrial depolarization, cytochrome c release, Bad, and caspase activation (221).

EPO also relies upon Wnt signaling that can control FoxO proteins to provide cellular protection. EPO protects against elevated glucose exposure in vascular endothelial cells by maintaining the expression of Wnt1 signaling (316). EPO enhances Wnt signaling to maintain the survival of mesenchymal stem cells (317), block Aβ toxicity in cerebral microglia (186), and maintain microglial cell integrity during oxidative stress (227). In other vascular systems that involve renal tissue, EPO prevents renal tubular cell apoptosis through

Wnt7b and β-catenin and by down-regulating specific micro-RNAs (miRNA) (318, 319). EPO employs Wnt signaling to reduce the activity of FoxO proteins and increase cell survival (93, 204). EPO uses Wnt1 to inhibit FoxO3a activity and maintain endothelial cell survival during elevated glucose (204).

4.3. Erythropoietin and mTOR

The pathways of of Akt and Wnt signaling employed by EPO also intersect with the mechanistic target of rapamycin (mTOR). mTOR also is known as the mammalian target of rapamycin and FK506-binding protein 12-rapamycin complex-associated protein 1 (116, 320). It is a 289-kDa serine/threonine protein kinase and is encoded by a single gene *FRAP1* (7, 321, 322). mTOR functions as a vital component in the protein complexes of mTOR Complex 1 (mTORC1) and mTOR Complex 2 (mTORC2) (116, 323). mTORC1 contains Raptor (Regulatory-Associated Protein of mTOR), the proline rich Akt substrate 40 kDa (PRAS40), Deptor (DEP domain-containing mTOR interacting protein), and mammalian lethal with Sec13 protein 8 (mLST8). mTORC2 has some of the same components of mTORC1 that include Deptor and mLST8, but also contains Rictor (Rapamycin-Insensitive Companion of mTOR), the mammalian stress-activated protein kinase interacting protein (mSIN1), and the protein observed with Rictor-1 (Protor-1) (11, 13).

The hamartin (tuberous sclerosis 1)/tuberin (tuberous sclerosis 2) (TSC1/TSC2) complex is an inhibitor of mTORC1 (6, 323). Although multiple regulatory phosphorylation sites are known to exist for TSC1, control of the TSC1/TSC2 complex can be regulated though pathways that include Akt and AMP activated protein kinase (AMPK) that phosphorylate TSC2 (13, 324, 325). Akt phosphorylates TSC2 on multiple sites that destabilizes TSC2 and disrupts its interaction with TSC1. Importantly, a limited reduction in TSC2 activity has been demonstrated to be necessary for cellular protection against Aβ to allow for mTOR activation, since complete knockdown of TSC2 can limit cellular protection (187). AMPK also phosphorylates TSC2 to inhibit mTORC1 activity (19, 326). In the nervous system, AMPK activation can limit Aβ production and secretion (327, 328), reduce oxidative stress parameters in diabetic animals with cognitive dysfunction (329), limit infarct size in models of stroke (330), be responsible for lifespan extension (331), may modulate neuroinflammation (332), and prevent memory impairment (193). Yet, AMPK activation is not consistently beneficial. The degree of AMPK activity is an important consideration, since in some experimental models involving cellular metabolism, AMPK activation promotes apoptotic cell death such as in pancreatic islet cells (333). In addition, excessive AMPK activation may lead to aberrant Aβ production (187, 327) and neuronal injury (334, 335). Pathways such as Wnt signaling can counteract the negative effects of AMPK. For example, WISP1 provides a minimal level of TSC2 and AMPK activity to control both cell survival and cell metabolism (187). WISP1 controls AMPK activation by differentially decreasing phosphorylation of TSC2 at Serine^{1387}, a target of AMPK, and increasing phosphorylation of TSC2 at Threonine^{1462}, a target of Akt (187). The ability of WISP1 to modulate AMPK activity also is important for the control of cellular metabolism (326).

EPO relies upon mTOR for neuronal cell development, differentiation, and survival (16, 76) (Table 1). EPO requires mTOR for the differentiation of neural precursor cells to achieve a

neuronal phenotype (336) and for the protection of retinal progenitor cells from oxidative stress (337). In models of sepsis-induced encephalopathy, protection against cognitive loss by EPO is lost during inhibition of mTOR pathways (229). EPO controls mTOR and its down-stream signaling pathways that involve PRAS40 to increase neuronal survival during oxygen-glucose deprivation (310). EPO, through mTOR and Wnt signaling, maintains microglial survival during oxidative stress (227). EPO can block Aβ toxicity through Wnt signaling and mTOR pathways as well to prevent caspase activation and apoptosis (186). During hypoxia-reoxygenation stress, EPO increases mTOR activity to protect hippocampus-derived neuronal cells (338). In the mTOR pathway, AMPK also may impact the biological function of EPO. The ability of EPO to oversee neuroinflammation may be linked to AMPK activity (166). EPO also may require a specific level of activation of AMPK to alleviate detrimental effects of oxidative stress (339). Yet, the concentration and activity of EPO may influence the protective actions of mTOR and signaling pathways associated with AMPK. High concentrations of EPO may increase cellular damage and lessen the activity of mTOR (340).

5. ERYTHROPOIETIN AND PROGRAMMED CELL DEATH

5.1. Apoptosis

EPO can block apoptotic cell death through multiple pathways that involve Akt activation, promotion of Wnt signaling, SIRT1 activity, modulation of the mTOR pathway, and inhibition of FoxO protein nuclear translocation and transcription. Apoptosis has an early phase that involves the loss of plasma membrane lipid phosphatidylserine (PS) asymmetry (175, 341, 342) that is followed by a later phase with DNA degradation (20, 343–346). Usually DNA destruction is considered a committed step, but reversal of membrane PS exposure can prevent microglial and macrophage engulfment of cells tagged with PS externalization (72, 204, 347–349).

Coupled to the onset of the apoptotic cascade can be the induction of oxidative stress and the generation of reactive oxygen species (ROS) (20, 258, 350, 351). ROS can lead to DNA destruction, senescence, organelle injury, protein misfolding, and neuronal synaptic dysfunction (41, 43, 52, 95, 149, 351, 352). For the most part, endogenous systems that include vitamins B, C, D, and K (54, 353–356) and glutathione peroxidase (356, 357) can prevent cellular injury during oxidative stress. Yet, pathology ensues when these systems are overwhelmed.

EPO can block apoptotic cell death under multiple conditions (Table 1). During ischemic reperfusion injury, EPO prevents tubular cell apoptosis through Wnt signaling pathways (318). In familial amyloidotic polyneuropathy, depressed levels of EPO may be associated with increased oxidative stress and apoptotic cell injury (358). EPO can prevent apoptotic injury against advanced glycation end-product (AGE) exposure in Schwann cells (359), sepsis (229, 360), cerebral ischemia (313, 345, 361), Aβ toxicity (186, 218, 358, 362–364), neuronal kainate-induced oxidative stress (26), vascular oxygen-glucose deprivation (194, 221, 310), hypoxia and anoxia (199, 365, 366), retinal disease (367, 368), experimental models of diabetes mellitus (194, 204, 314, 316, 369, 370), and toxins that destroy microglial cells (146, 166, 186, 227, 368).

In relation to blocking the detrimental effects of oxidative stress and ROS, EPO protects endothelial cells (144, 194, 199, 203, 204, 214, 220, 221, 316, 368, 371–376), neurons (26, 210, 237, 345, 362, 377–382), astrocytes (377, 383–385), and microglia (166, 186, 196, 227, 368, 381). During oxidative stress, EPO also preserves neurogenesis (336, 386), stem cell development (126, 220, 237, 312, 372, 387), and promotes erythroid progenitor cell development with the modulation of FoxO3a activity (29, 169, 237, 307). EPO can prevent free radical cell injury (210, 215, 371, 388–390) through the blockade of ROS generation (212, 339, 370, 381, 391).

5.2. Autophagy

In addition to apoptosis, autophagy is another pathway of programmed cell death that is controlled by EPO. Autophagy recycles components in the cell cytoplasm to remove non-functional organelles for disposal and tissue remodeling (14, 342, 392, 393). Autophagy is classified as microautophagy, chaperone-mediated autophagy, and macroautophagy (122). Macroautophagy is the principal category of autophagy and consists of the sequestration of cytoplasmic proteins and organelles into autophagosomes. Autophagosomes combine with lysosomes for degradation and recycling (122, 393–396). Microautophagy leads to the invagination of lysosomal membranes for the sequestration and digestion of cytoplasmic components. Chaperone-mediated autophagy uses cytosolic chaperones for the transport of cytoplasmic components across lysosomal membranes (6).

EPO can block autophagy through the activation of mTOR (16, 397, 398) (Table 1). Activation of mTOR blocks autophagy by phosphorylating autophagic related genes (*Atg*) and proteins that include Atg13 and ULKs to inhibit the UNC like kinase complex ULK-Atg13-FIP200 (7). EPO, Akt, and mTOR activation protect against increased activity of autophagy in epithelial cells (213) and promote protection against hypoxia and oxidative stress in retinal progenitor cells (337). EPO controls excessive autophagy that precedes apoptosis during experimental neonatal necrotizing enterocolitis (213). EPO also can modify the activity of autophagy and limit neonatal brain damage in the developing rodent during hyperoxia exposure and oxygen toxicity (399). Under some experimental conditions in neuronal cell line models, EPO can suppress apoptotic cell injury through the increased activity of AMPK and limited autophagy activity (400).

6. ERYTHROPOIETIN AND CLINICAL EFFICACY

The remarkable progress in understanding the protective signaling pathways of EPO has provided fertile ground for the launch of several clinical studies evaluating the protective role of EPO in the nervous system. At present, more than 60 ongoing or completed clinical trials are listed on the National Institutes of Health website ClinicalTrials.gov for EPO and disorders of the nervous system. In recent trials, new information has been gained to translate the findings of basic research for EPO in the nervous system into potential clinical utility.

EPO may provide neuroprotection against developmental impairment in preterm infants (Table 1). EPO has been reported to offer developmental cognitive support in humans with the observation that elevated EPO concentrations during infant maturation have been

correlated with increased Mental Development Index scores (401). In a randomized, double-blind placebo-controlled study involving preterm infants, recombinant EPO (3000 IU) was administered before 3 hours of age, at 12–18 hours of age, and 36–42 hours of age. EPO was demonstrated to improve white matter development assessed by diffusion tensor imaging and tract-based spatial statistics (400). Other work has supported that EPO (3000 IU) administered within 42 hours of age in preterm infants reduced the risk of brain injury assessed by magnetic resonance imaging (402).

However, the neuroprotective ability of EPO may have greater utility in the immature brain than compared to the adult brain with severe dysfunction. In a randomized trial of 200 patients with closed head injury and the inability to follow commands, EPO (500 IU/kg) was administered for 3 days then weekly for 2 weeks in the setting of maintaining hemoglobin concentration of greater than 10 g/dL. Following the completion of the study, EPO or maintaining hemoglobin concentration of greater than 10 g/dL did not result in improved neurological outcome at 6 months (403). Studies with patients suffering from ischemic stroke and receiving human choriogonadotropin alfa followed by EPO also did not show improvement in neurological recovery (404).

Yet, in a study with long-term administration of the biosimilar epoetin α (Binocrit) in elderly patients with myelodysplastic syndromes, cognitive function appeared to improve that may be related to resolution of anemia (405). In a limited study with 26 PD patients, recombinant EPO administration improved cardiovascular autonomic dysfunction and cognition, but did not affect motor function of the patients (406). In relation to the cardiovascular benefits potentially gained from EPO, several studies suggest that at least high concentrations of EPO may not be warranted to protect cardiac function (142, 168, 407–409). Yet, some work indicates that low concentrations of EPO may be beneficial to the cardiovascular system (212, 360, 410) which could subsequently benefit neurological function.

7. FUTURE CONSIDERATIONS FOR ERYTHROPOIETIN

With the increased life expectancy of the global population, the incidence of acute and chronic neurodegenerative disorders is expected to increase. Presently, more than 30 million individuals suffer from disorders of the nervous system throughout the world (4, 5). EPO and its signaling pathways offer exciting prospects for the treatment of neurodegenerative disorders. EPO governs a number of critical pathways that support cells of the nervous system to include Akt, sirtuins, Wnt signaling, and mTOR. In addition, EPO has been shown to impact programmed cell death pathways that involve apoptosis and autophagy and target specific “pro-apoptotic” proteins such as forkhead transcription factors. Translational of the critical cellular pathways involving EPO into effective clinical treatments for the nervous system has been promising for fetal brain injury. Additional work is necessary to determine the role of EPO for treatment of the adult brain that involves trauma, cognition, ischemic brain disease, related cardiovascular disease, and degenerative disorders of the nervous system. Outcomes from these studies can be heavily influenced by multiple factors that include EPO concentration, timing of administration, onset and severity of the underlying disorder, and the targeting of specific down-stream pathways for EPO.

Yet, use of EPO as a clinical neuroprotective entity brings with it a number of considerations. EPO is a growth factor and controls cellular proliferative pathways that can lead to tumorigenesis. EPO (411–413) and pathways that involve Akt (414–416), mTOR (417–419), and Wnt signaling (268, 271, 279, 288, 420) can promote unchecked tumor growth. EPO also may be involved with the self-renewal of tumor-initiating cells (421).

EPO may have detrimental vascular effects and be contraindicated under specific circumstances, such as in patients with poorly controlled hypertension, individuals with known blood viscosity concerns, and in those with diabetic complications of the nervous system. EPO can limit FoxO activity in addition to other pathways to reduce ischemic stroke size (313). Yet, EPO may increase the risk of vascular complications in the brain. EPO administration results in a two-fold increase in stroke that is not attributed to any baseline characteristic or to blood pressure, hemoglobin, platelet count, or treatment dose of EPO in patients with diabetes mellitus and renal disease (422). Blood viscosity has been reported to be increased with a reduction in cerebral blood flow in mice that overexpress EPO (423). EPO also can increase vascular responsiveness (424) and may lead to hypertension (29, 142, 425). For the retina, elevated EPO concentrations may be associated with proliferative diabetic retinopathy (426) that is tied to excessive microvascular angiogenesis. Sustained erythrocytosis with EPO also may activate inflammatory pathways and result in blood-brain barrier dysfunction (427).

Focusing upon the cellular signaling pathways of EPO could potentially enhance clinical efficacy for the treatment of neurodegenerative disorders and limit unwanted side effects for EPO. For example, targeting pathways of EPO, such as mTOR, that can finely control the activity of apoptosis and autophagy may foster significant benefit for the treatment of cognitive neurodegenerative disorders. In microglial cells of the nervous system, Aβ can inhibit mTOR signaling through PRAS40 (186, 428) that leads to apoptosis and may foster disease progression during Aβ toxicity. EPO, through the activation of mTOR can limit PRAS40 activity and block apoptotic cell injury (310). Increased mTOR signaling also may necessary to regulate the β-site amyloid precursor protein (APP)-cleaving enzyme 1 (β-secretase, BACE1) that promotes Aβ accumulation in AD, since elevated mTORC1 activity reduces BACE1 and is able to limit Aβ generation (429). In animal models of AD, loss of mTOR signaling has been shown to impair long-term potentiation and synaptic plasticity that can be reversed with the up-regulation of mTOR signaling (430). Conversely, other work suggests that some degree of inhibition of mTOR may be necessary to enhance Aβ clearance and improve spatial learning through the activation of autophagy (431). Future work that recognizes the fine interplay of the signaling pathways of EPO could yield the greatest benefits for the successful treatment of multiple disorders in the nervous system.

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Table 1

Regenerative and Protective Properties of EPO in the Nervous System

Property	Function
EPO Structure	The integrity of EPO, a 30.4 kDa protein, is dependent upon the structure and the maintenance of the oligosaccharide side chains
	The oligosaccharides and the glycosylated chains protect EPO from free radical oxygen degradation
EPO Production	EPO expression is regulated by changes in oxygen tension
	HIF-1 modulates the expression of EPO and EPOR
	EPO production can be affected by other entities such as trophic factors, metabolic changes, infection, cytokines, selenium, and neuronal depolarizations
EPO Signal Transduction Pathways	EPO phosphorylates and activates Akt to lead to cytoprotection, reduce inflammation, and prevent oxidative stress mediated injury injury
	EPO controls the nuclear translocation and the post-translational processing of FoxOs to prevent the induction of “pro-apoptotic proteins
	EPO employs SIRT1 to maintain cellular energy homeostasis and control cellular differentiation
	EPO relies upon Wnt/WISP1 signaling to foster stem cell survival, block FoxO protein activity, prevent cellular injury during toxin exposure, and maintain the integrity of non-neuronal cells in the nervous system
	EPO relies upon mTOR for neuronal cell development, differentiation, and survival
	EPO controls mTOR and its down-stream signaling pathways that involve PRAS40 and AMPK to promote stem cell development, cell differentiation, and cell survival
EPO, Apoptosis, and Autophagy	EPO can prevent apoptotic injury during oxidative stress against multiple injuries such as advanced glycation end-product exposure, Aβ toxicity, and hypoxia
	EPO can block autophagy through the activation of mTOR. Under some conditions, EPO can suppress apoptotic cell injury through increased AMPK and autophagy activity
EPO Clinical Efficacy	EPO may provide neuroprotection against developmental impairment in preterm infants and offer cognitive improvement in elderly patients with myelodysplastic syndromes
	EPO may assist with protection against neurological impairment through improved cardiovascular function

Akt: protein kinase B; Aβ: beta-amyloid; AMPK: AMP activated protein kinase; EPO: erythropoietin; EPOR: erythropoietin receptor; FoxO: mammalian forkhead transcription factors of the O class; HIF-1: Hypoxia-inducible factor 1; mTOR: mechanistic target of rapamycin; PI 3-K: Phosphoinositide 3-kinase; PRAS40: the proline rich Akt substrate 40 kDa; SIRT1: silent mating type information regulation 2 homolog 1 (*S. cerevisiae*); WISP1: wnt1 inducible signaling pathway protein 1; Wnt: proteins derived from the *Drosophila Wingless* (*Wg*) and the mouse *Int-1* genes