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The effect of erythropoietin on cardiac and neurotoxicity induced by carbon monoxide poisoning

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ABSTRACT

Carbon monoxide (CO) intoxication is one of the most important poisonings related to high morbidity and mortality rate. The main treatment of CO poisoning is oxygen therapy using normobaric (NBO) or hyperbaric oxygen (HBO). However, more pharmaceutical agents are needed to improve CO poisoning treatment, especially in severe cases. Recently, erythropoietin (EPO) has been examined in several studies, showing a significant reduction in cardiac and neural sequels of CO poisoning.In this article, the effect of EPO on cardio and neurotoxicity of CO poisoning were reviewed. For this purpose, EPO effect on CO poisoning was searched in papers published until 2020 using Pubmed, Scopus, and google scholar. Only English papers on three main databases have been reviewed. The review of several animal and clinical studies have been shown that EPO administration after CO poisoning could improve neurological function and reduce CO-neurotoxicity significantly. Although there is good evidence of EPO effects on CO-induced-neurological sequelae, further clinical studies are needed to establish its benefit on CO intoxication.

Keywords:
Carbon monoxide poisoning
Erythropoietin
Cardiotoxicity
Neurotoxicity

Introduction

Carbon monoxide (CO) is a highly toxic, odorless, tasteless, and colorless gas produced by incomplete combustion of hydrocarbon fuels. Smoking, Car exhaust, faulty heater, fire, and industrial emissions are the common sources of CO (Eichhorn et al., 2018; EJ 2007; Lippi et al., 2012). Unfortunately, CO intoxication remains a common type of poisoning leading to high morbidity and mortality worldwide especially in developing countries while a new study in Iran has reported 763 death annually related to CO poisoning (Kinoshita et al., 2020; Hosseininejad et al., 2018).

Acute CO poisoning caused by high CO concentration is a leading cause of life-threatening conditions with major cardiac and neurological insults (Rose et al., 2017). Carbon monoxide binds to the hemoglobin and reduces the oxygen binding capacity which is resulted in tissue hypoxia. CO also interacts with other heme molecules

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such as cytochrome oxidase and myoglobin. Also, it interferes with oxygen consumption and heart contractile function (Kinoshita et al., 2020; Rose et al., 2017). A wide range of cardiac insults have been reported in acute CO poisoning including; cardiac arrhythmia, hypo and hypertension, cardiac ischemia, and in severe cases; cardiac arrest (Gandini et al., 2001; Rose et al., 2017). Also, depending on the severity of poisoning different brain consequences have been shown; from headache and dizziness to comma, brain ischemia, and death (Rose et al., 2017; Wu and Juurlink, 2014).

Given the pathophysiology of CO poisoning, Oxygen therapy is the main treatment for CO intoxication. However other pharmaceutical agents are needed to complete recovery, especially in severe intoxication.

Recently, Erythropoietin (EPO), a hematopoietic cytokine, has been investigated extensively for new effects such as tissue-protective and anti-ischemia properties (Nekoui and Blaise, 2017; Paschos et al., 2008; Peng et al., 2020). EPO in adults is mainly produced by the kidney in response to hypoxia then through its receptor (EPOR), prevents programmed cell death in erythrocyte precursors and maintains red blood cell mass (Peng et al., 2020). However, there is evidence indicating EPO is produced by many tissues in response to cell stress and hypoxia. In addition, EPOR has been found in other organs such as placenta, retina, skin, and heart. It has been shown during hypoxic conditions, local EPO production is induced by Hypoxia-inducible factor (HIF) (Nekoui and Blaise, 2017; Peng et al., 2020). However, the maximum tissue-protective effect is not achieved by induced EPO because of a delay in EPO production after injury and also, inhibition of EPO gene expression by inflammatory cytokines such as tumor necrosis factor- α (TNF-α). Otherwise, many animal and clinical studies have shown administration of exogenous EPO resulted in obvious anti-ischemic and tissue-protective effects, especially in heart and brain tissues (Ghezzi and Brines, 2004; Paschos et al., 2008; Santhanam et al., 2010).

Based on the hypoxic/ischemic insults induced by CO poisoning and on the other hand the anti-ischemia/ tissue-protective effects of EPO, it seems EPO could reduce the CO poisoning consequences especially cardiac and neurologic consequences. In this regard, several studies have investigated EPO effects on CO-induced cardio and neurotoxicity.

The present article reviewed the proposed implication of EPO in CO poisoning. Also, its potential therapeutic provides information on possible mechanisms for this action.

CO toxicity

CO toxicity mechanism

The well-known mechanism of CO toxicity is binding to hemoglobin with more affinity than oxygen and formation of carboxyhemoglobin (COHb) which is resulted in impaired oxygen delivery and tissue hypoxia. Moreover, CO interferes with aerobic metabolism in mitochondria through binding to cytochrome oxidase and induces an inflammatory response by neutrophil activation and free radical production leading to lipid peroxidation, oxidative stress, and finally apoptosis cell death (EJ, 2007; Rose et al., 2017).

Clinical symptoms of CO poisoning

Since cardiac and neurologic tissues have more oxygen demand, they are more susceptible to hypoxia-induced by CO poisoning (Chiew and Buckley, 2014; Dubrey et al., 2015). Arrhythmia, cardiac ischemia, hypertension, infarction, and cardiac arrest have been shown following acute CO intoxication (Gandini et al., 2001; Henry et al., 2006). Moreover, several cohort studies have indicated an increase in cardiovascular events in long term following CO poisoning. They have shown a higher risk of cardiac arrhythmia, myocardial injury, and hypertension in CO intoxicated compared to the normal population (Eichhorn et al., 2018; Henry et al., 2006).

In addition, CNS signs and symptoms are predominant after CO poisoning and appear immediately after intoxication as persistent neurological sequelae (PNS) such as headache, dizziness, loss of conciseness, seizure, and coma. In some cases, CO-neurotoxicity signs occur after weeks as delayed neurologic sequelae (DNS) including peripheral neuropathy, motor dysfunction, vestibular abnormality, neurophysiologic disturbances, and Parkinsonism (Guzman, 2012; Oh and Choi, 2015; Weaver, 2009). In this regard, several studies revealed the relation between CO poisoning and the higher risk of Parkinson's incidence. For instance, based on reports, It seems that CO poisoning caused substantia nigra injury (Choi, 2002; Kao et al., 2012; Lai et al., 2015).

CO poisoning treatment

Oxygen therapy is the main treatment of CO poi-

soning, using 100% normobaric oxygen (NBO) or hyperbaric oxygen (HBO) (EJ, 2007; Weaver, 2009). Although HBO benefits in CO poisoning are controversial, it is recommended for severe CO poisoning including coma, seizer, serious cardiac and neurological deficits, pregnancy as well as high level of COHb (Eichhorn et al., 2018; Prockop and Chichkova, 2007; Rose et al., 2017; Wu and Juurlink, 2014). However, besides oxygen therapy, other pharmaceutical agents also have been administrated for severe CO-cardio and neurotoxicity (Rose et al., 2017).

EPO

EPO is a hematopoietic cytokine produced by the kidney in response to hypoxia and used potentially for the management of anemia in chronic renal disease and cancer chemotherapy (Jelkmann, 2004). However, EPO has been found also in the brain, and EPO receptors are observed in other sites such as endothelial cells, heart, central nervous system, placenta, adipose, and skin tissues (Sasaki, 2003) indicating other effects of EPO than erythropoiesis.

EPO and tissue-protective effect

Besides to well-known EPO hematopoiesis effect, there are numerous pieces of evidence indicating the tissue-protective and anti-ischemia properties of EPO (Ghezzi and Brines, 2004; Joyeux-Faure et al., 2005; Paschos et al., 2008). For this purpose, EPO has been investigated for new effects in many studies and examined extensively in the brain and cardiac ischemia also liver, skin, and retina injuries (Nekoui and Blaise, 2017; Ghezzi and Brines, 2004; Aghdam et al., 2016; Paschos et al., 2008). It seems that the new effects of EPO are mainly mediated by its anti-apoptosis, anti-inflammatory, and anti-oxidative properties (Burger et al., 2009; Jelkmann, 2004; Katavetin et al., 2007; Paschos et al., 2008).

The neuroprotective effect of EPO

It is well-described that EPO has neuroprotective effects and improves brain function in ischemia/reperfusion injury (Aydin et al., 2003; Dame and Christensen, 2001; Paschos et al., 2008). According to several studies, this neuroprotective effect is implicated through inhibition of glutamate release and interfering with the intracellular calcium concentration along with other EPO mechanisms such as anti-apoptosis effect (Nekoui and Blaise, 2017; Nguyen et al., 2014).

Besides *in vivo* studies, the benefit of EPO in brain ischemia has been established in several clinical trials (Simon et al., 2019; Ehrenreich et al., 2002). Also, the efficacy of EPO administration has been shown in neurodegenerative diseases such as Parkinson's, Alzheimer and multiple sclerosis(Nekoui and Blaise, 2017).

The cardio-protective effect of EPO

The cardio-protective effect of EPO has been examined in numerous studies indicating EPO effects in reduction of infarct size and improved left ventricular function in cardiac ischemia injury (Mastromarino et al., 2013; Santhanam et al., 2010). This cardio-protective effect is mediated mainly by anti-apoptosis and anti-inflammatory properties as well as promoting angiogenesis and mobilizing endothelial progenitor cells (Burger et al., 2009; Joyeux-Faure et al., 2005). Moreover, the administration of EPO, in heart failure patients with anemia resulted in improved ejection fraction and reduced left ventricular hypertrophy (Silerberg et al., 2005).

Despite the results of animal studies, EPO efficacy in cardiac ischemia and acute myocardial infarction has not been confirmed by clinical trials yet. Also, some studies have reported the platelet activation effect of EPO that could interfere with the safety and efficacy of EPO on cardiac ischemia (Roubille et al., 2013). Eventually, it seems that further studies are needed to elaborate on the exact EPO effect on human myocardial infarction.

Molecular Mechanisms of EPO protective effects

EPO exerts its hematopoietic effects through binding to its well-known receptor; EPOR. a receptor-associated Janus kinase-2 (Jelkmann 2004). However, there is evidence representing the tissue-protective effect of EPO performed via heterodimer of EPOR and beta common receptor (βCR) which is called tissue-protective receptor (TPR) (Peng et al., 2020) (Figure 1). Binding of EPO or its derivatives to TPR leads to tyrosine phosphorylation of cytosolic domain of receptor and activation of several signaling pathways such as Janus tyrosine kinase 2 (Jak2) and secondly Signal transducer and activator transcription (STAT) which mediate activation of anti-apoptotic molecules like Bcl_2 and inhibition of pro-apoptotic proteins like Bcl_2 associated X protein (Bax) (Jelkmann, 2004; Paschos et al., 2008). It seems

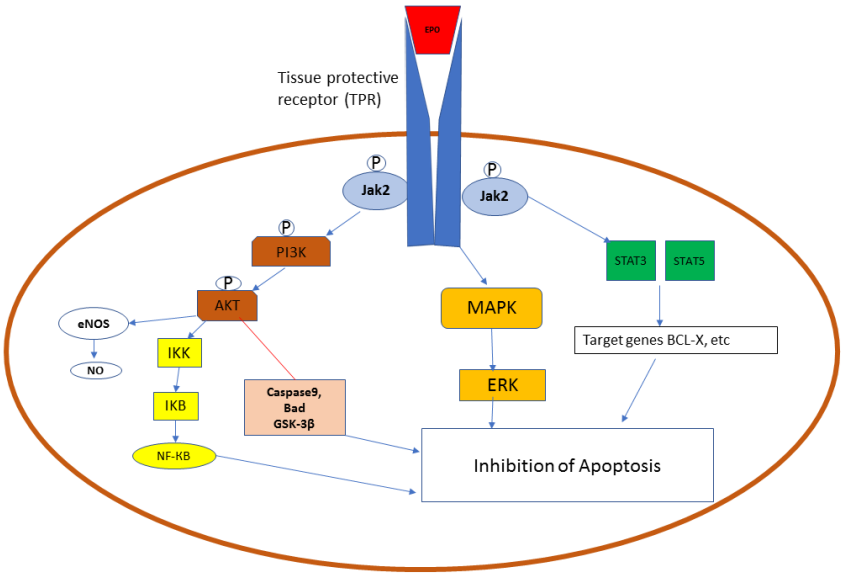

FIGURE 1. Schematic of signal transduction pathways of erythropoietin (EPO). Binding the EPO to the tissue protective receptor (TPR) results in activation of Janus tyrosine kinase 2 (Jak2) through phosphorylation leading to activation of three pathways; Induction of Signal transducer and activator transcription 3,5(STAT3) and (STAT5) results in upregulation survival signals. Another cascade is: phosphatidylinositol 3 kinase/protein kinase b (PI3K/AKT) which inhibit apoptosis through different signals. The third cascade is Mitogen Activated protein Kinase (MAPK) which also inhibits GSK3β and attenuate inflammation (Alireza Nekoui 2017; Peng et al., 2020).
BAD: BCL2 associated agonist of cell death), Bcl-2 (B-cell lymphoma 2), ERK: extracellular signal-regulated kinase, GSK3β: glycogen synthase kinase-3β, IKK: inhibitor of nuclear factor-κB kinase, IKB: inhibitor of nuclear factor-κB, NF-κB: nuclear factor-κB.

this pathway has a main role in EPO anti-apoptosis effect (Nekoui and Blaise, 2017; Peng et al., 2020).

The other pathway, involved in the tissue-protective effect of EPO, is phosphatidylinositol 3 kinase (PI3K) /AKT (Burger et al., 2009; Ghezzi and Brines, 2004; Jelkmann, 2004). It is well known that PI3K /AKT pathway has a role in cell-death inhibition via the inactivation of several pro-apoptotic molecules such as caspase 9, glycogen synthase kinase-3β (GSK-3β), and increase nitric oxide production by activation of eNOS (Burger et al., 2009; Paschos et al., 2008). PI3K /AKT pathway also has a mediatory role in the opening of mitochondrial K_{ATP} channels which are involved in the stability of mitochondrial membrane potential (Shi et al., 2004). Another considered mechanism of EPO protective effect is the activation of mitogen-activated protein kinases (MAP Kinases), the well-known pathway for apoptosis inhibition. Also, activation of nuclear factor-κB (NF-κB) has been demonstrated via the JAK2 pathway which is involved in the reduction of inflammation, oxidative injury, and apoptosis. (Lawrence, 2009)

Finally, besides the role of EPO in the activation of antioxidant enzymes (superoxide dismutase, catalase, glutathione peroxidase), EPO acts as an oxidant-scavenger and anti-oxidative agent directly (Katavetin et al., 2007; Paschos et al., 2008).

EPO in CO poisoning

Considering the hypoxic/ ischemic injury in CO poisoning and the evidence of tissue-protective and anti-apoptosis effects of EPO, the efficacy of EPO has been evaluated on CO poisoning in several basic and clinical studies (Table 1).

EPO effects on CO-cardiotoxicity

The EPO effect on CO-cardiotoxicity has been evaluated in an *in vivo* study. EPO (5000 IU/Kg) was administrated in rats that were intoxicated by 250, 1000, and 3000 ppm of CO. The results of this study showed that EPO significantly decreases CO-induced myocardial injury and apoptosis cell death in rats (Rezaee and Mohammadpour, 2016). Moreover, their results represented that EPO administration after CO poisoning reduces electrocardiogram (ECG) abnormality compared to non-receiving EPO animals. For this purpose, they showed that ST depression, ST elevation, T wave inversion, and PR prolongation disappeared in EPO-receiving animals (Asgharian Rezaee et al., 2012).

EPO effects on CO-neurotoxicity

TABLE 1: Animal and clinical studies show erythropoietin (EPO) effect on carbon monoxide (CO) poisoning.

Type of Study	Organ target	Dosage of EPO	CO poisoning severity/ model	EPO effects	References
In vivo (Rat Species)	Brain	Single dose: 5000 IU/Kg following acute CO intoxication (IP*)	3000 ppm CO for 1 hour	Reduction of serum brain biomarker; S100β	(Shahsavand et al., 2012)
In vivo (Rat Species)	Brain	Single dose: 2000, 5000, and 10,000 IU/Kg following acute CO intoxication (IP)	3000 ppm CO for 1 hour	Preserve the integrity of the blood-brain barrier, decrease lipid peroxidation in brain tissue and myeloperoxidase activity	(Moallem et al., 2015; S. Shahsavand, 2012)
In vivo (Rat Species)	Heart	Single dose: 5000 IU/Kg following acute CO intoxication (IP)	250, 1000, and 3000 ppm CO for 1 hour	Reduction of ECG abnormality (PR prolongation, T wave inversion, and ST changes)	(Asgharian Rezaee et al., 2012)
In vivo (Rat Species)	Heart	Single dose: 5000 IU/Kg following acute CO intoxication (IP)	3000 ppm CO for 1 hour	Inhibition of CO-induced apoptosis in cardiac cells and reduction of myocardial injury	(Rezaee et al., 2017; Rezaee and Mohammadpour, 2016)
In vivo (rat Species)	Brain	Multiple doses: 2500 and 5000 IU/Kg twice a day for 2 days following CO intoxication (IP)	1000 ppm for 1 hour followed by 3000 ppm until induction of unconsciousness	Inflammatory cytokine reduction in hippocampal tissue (NF-κB, TLR4, TNF-α, IL1, IL6)	(Pang et al., 2016)
Case report; two patients	Brain	10,000 IU every other day, for 3 times And 10,000 IU every 5 days for 3 times (SC**)	Two severe CO intoxicated patients: A 16 years old woman And 19 years old man	Treatment of acute and delayed encephalopathy induced by CO poisoning	(Li et al., 2009)
Clinical trial; 103 patients	Brain	10,000 IU every day for one week (SC**)	CO intoxicated patients > 16 years 54 patients received EPO 49 patients received normal saline	Acceleration of CO induced-neurologic sequelae; Improve brain function (Barthel index), reduce S100β and delayed encephalopathy	Pang et al.,) (2013

*Intra-peritoneal injection
**subcutaneous injection

Shahsavand *et al*. evaluated the effect of EPO on CO-neurotoxicity in animal models. In this study, different doses of EPO (2500, 5000, 10,000 IU/Kg) were injected immediately in rats that were intoxicated by 3000 ppm CO. The results showed that single administration of EPO after acute CO intoxication significantly reduces brain lipid peroxidation, as well as myeloperoxidase brain activity, and also decreases serum level of S100β induced by acute CO poisoning in animals (Shahsavand, 2012; Shahsavand et al., 2012). In addition, reduction of Bax/Bcl2 ratio in brain tissue and restoration of blood-brain barrier integrity were shown by EPO administration in this study (Moallem et al., 2015). In another experimental study, Li Pang et al. (2016) studied the anti-inflammatory mechanism of EPO in acute CO poisoning. In their study, acute CO poisoning in animals was induced by 1000 ppm followed by 3000 ppm CO. EPO (2500, 5000 IU/Kg) was injected after acute CO poisoning, twice daily for two days in rats. According to their results, EPO attenuates the expression of Toll-like receptors (TLR4), nuclear factor kappa B (NF-κB), and other inflammatory cytokines in rat hippocampal tissue in comparison with animals that did not receive EPO (Pang et al., 2016).

Regarding these animal studies, it seems EPO via its anti-inflammatory, anti-oxidative, and anti-apoptosis properties could be effective in the treatment of CO-neurotoxicity (Moallem et al., 2015; Pang et al., 2016; Shahsavand et al., 2012).

Also, there is a case report by Ying Li et al. that erythropoietin has been administrated to two severe CO poisoned patients; 19 and 70 years old. In this study, EPO was administrated at 10,000 IU three times which was well tolerated by patients. According to their results,

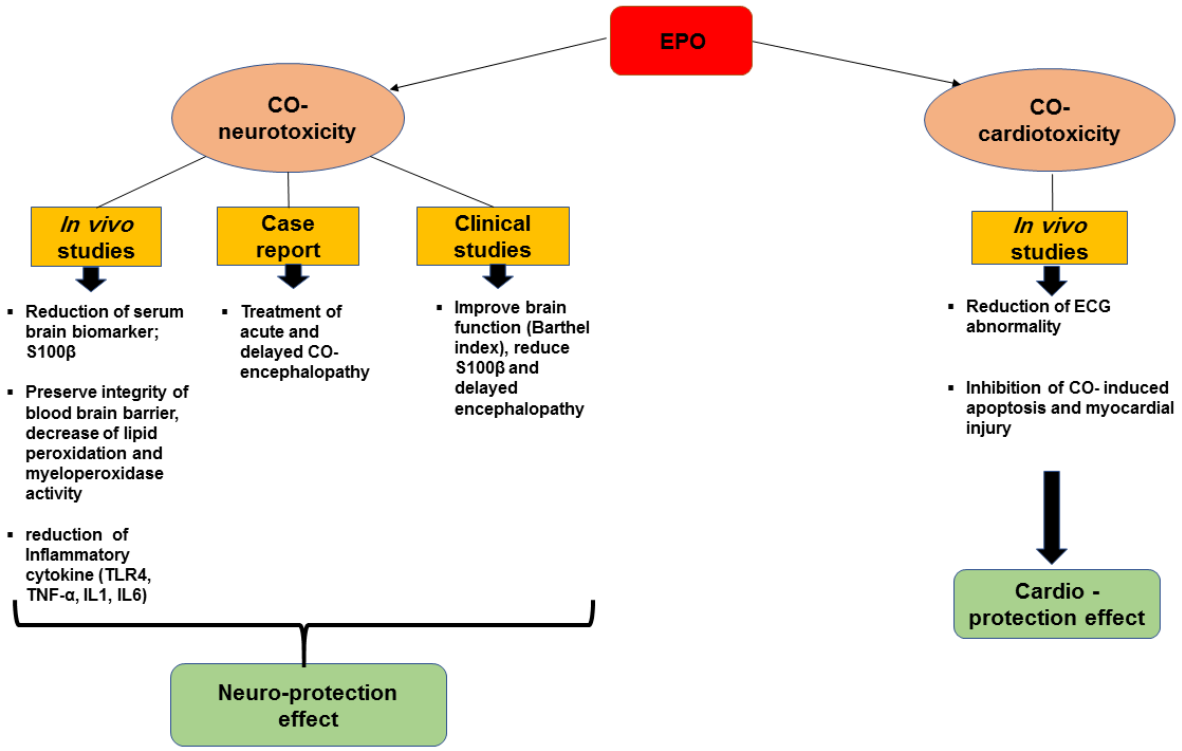

FIGURE 2. In this study, the EPO effects on CO-cardio and neurotoxicity were reviewed. The cardiac effect of EPO on CO toxicity has been examined in two in-vivo studies. The results showed that EPO administration reduces ECG abnormality and cardiac injury induced by CO intoxication. Moreover, several in-vivo and clinical studies have evaluated the effect of EPO on CO-neurotoxicity. Following EPO treatment, In-vivo studies have reported the reduction of serum brain biomarkers, preservation of the blood-brain barrier, and decrease of inflammatory cytokines. Also, improvement in brain function and decline of delayed encephalopathy have been demonstrated in clinical studies.

the mental ability was recovered and the manifestation of Parkinsonism was dispreaded by using EPO. In this study, they showed EPO effectively treates acute and delayed encephalopathy (Li et al., 2009).

Recently, in a clinical trial by Li Pang et al. EPO (10,000 IU/ day for one week) was administrated in CO poisoned patients and its neuroprotective effects were evaluated for 30 days. They implicated that EPO significantly improves neurological function (Barthel index), reduces brain biomarkers (S100β), and decreases the risk of DNS in patients receiving EPO (Pang et al., 2013). The outcome of this trial shows the efficacy of EPO in CO-neurotoxicity.

In overall, the reviewed studies have shown the significant EPO effect on brain injury/ischemia induced by CO poisoning. It seems EPO could be considered as a treatment for CO-neurotoxicity. However more clinical trials are needed to confirm the effect of EPO on CO poisoning.

Conclusion

Nowadays CO poisoning remains a leading cause of poisonous death. Therefore several pharmaceutical agents have been investigated for improving CO poisoning treatment in the last decades; among these studies, animal and clinical evidence shows that EPO could reduce the consequences of CO poisoning, especially neurotoxicity via its anti-apoptosis, anti-inflammatory, and anti-oxidative effects. Although there are clinical pieces of evidence that support EPO effectiveness in CO-neurotoxicity, further studies are needed to establish the EPO benefit in CO poisoning.

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Declaration of interest

There is no conflict of interest in this study.

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