

# Carbon monoxide as a promising molecule to promote nerve regeneration after traumatic brain injury

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## Abstract

Carbon monoxide (CO) is known as a toxic gas. Although there have been many studies on both toxic and protective effects of CO, most of these studies lack novelty, except for Eng H Lo team's study on the therapeutic effect of CO on brain injuries. In this commentary, we summarize the potential application value of CO in the treatment of some clinical diseases, especially its protective effect and nerve regeneration in brain injuries, hoping that our interest in CO could promote related clinical application studies.

**Key words:** carbon monoxide; toxicity; anti-inflammatory; neural stem cell; pericyte; traumatic brain injury; protection; hydrogen

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Carbon monoxide (CO) is known as a poisonous gas and only a low concentration can be fatal.<sup>1</sup> Aristotle (384–322 BC) first recorded that burning coals emanated toxic fumes. CO gas was used to execute prisoners in ancient Europe by burning coal in a closed bath room. CO was first prepared artificially by the French chemist de Lassone in 1776 by heating zinc oxide with coke, although he mistook it as hydrogen at the time because he noticed a blue flame similar to that of hydrogen combustion during the burning process. In 1800, the British chemist William Cruikshank proved that CO was composed of carbon and oxygen. Subsequently, the French physiologist Claude Bernard made a thorough study about the toxicity of CO. He firstly put forward the concept of the blind experiment method, and also firstly discovered that vegetarian diets produced alkaline substances and meats could increase acid metabolites. In 1846, Bernard subjected the dog to CO inhalation and found that the dog's blood became "more bright red than any of the arterial blood". This "cherry red" blood is later known as the characteristic

symptom of CO poisoning.<sup>2,3</sup>

Numerous studies have proved that CO gas is similar to nitric oxide,<sup>4</sup> a kind of cell second messenger and nerve regulation molecule. A very low concentration of CO can produce physiological functions, especially in neural function adjustment<sup>5</sup> and vascular relaxation.<sup>6</sup> CO also plays an important role in the process of pathophysiology in many diseases, including neurodegenerative diseases, hypertension, heart failure and various types of inflammation. CO can play an anti-inflammatory role<sup>7</sup> by inhibiting the motion of white blood cells, promoting their bacterial phagocytosis, and inhibiting white blood cells to release inflammatory cytokines. Animal studies have demonstrated that CO can be used to treat sepsis,<sup>8</sup> acute pancreatitis,<sup>9</sup> liver ischemia/reperfusion injury,<sup>10</sup> colitis,<sup>11,12</sup> osteoarthritis,<sup>13</sup> lung injury,<sup>14</sup> heart-lung transplantation rejection<sup>15</sup> and neuropathic pain,<sup>16-18</sup> and promote skin wound healing,<sup>19</sup> which is more familiar to us, isn't it? Besides, Yabluchanskiy et al.<sup>20</sup> has demonstrated carbon monoxide-releasing molecule-3



(CORM-3) promote neuroprotection or neurotoxicity after experimental intracerebral hemorrhage depending on the time of administration. This effect is due to its anti-inflammatory effect.<sup>21</sup> Liu et al.<sup>22</sup> has hypothesized that electrical acupuncture treatment on perinatal hypoxic-ischemic brain damage in rats increases cortical CO content to protect against hypoxic damage *via* the hydrogen sulfide/CBS–CO/HO-1–HIF-1 $\alpha$  system. Ample evidence indicates that CO is a physiological anti-inflammatory factor. Inhalation of CO or CO-releasing molecules can be used as a treatment for histological inflammatory reaction.

Although research on the effects of CO is appreciable, most related studies lack novelty. But a recent research paper by Eng H Lo group from Massachusetts General Hospital in USA published on the *Journal of Natural Medicine* reported their use of CO in the treatment of traumatic brain injuries (TBI), which is a reflection of the activity and influence of this research group in this field.<sup>23</sup> They found that the CO-releasing molecule CORM-3 could reduce vascular pericyte death of the brain tissue after brain injury and protect neurobehavioral functions. Pericytes, which are also known as Rouget cells or perivascular cells, are surrounded by capillaries and venous endothelial cells all over the body. Studies using free radical scavenger N-tertiary-butyl-alpha-phenyl nitrate (PBN) as control proved that PBN could also reduce pericyte death but was unable to improve the nerve function, which is the highlight and novel finding of Eng H Lo group.

They also found that CORM-3 could increase the phosphorylation level of neuronal nitric oxide synthase in neural stem cells, which was not observed in either the control group or PBN treatment group. CO exerted its effect *via* nitric oxide by regulating the phosphorylation of nitric oxide synthetase.<sup>24,25</sup> CORM-3 could increase the quantity of both NeuN and BrdU positive cells in the body, indicating that it could promote the proliferation of neural stem cells in the brain. Inhibiting the activity of nitric oxide synthase could reverse the effect, and also interfere with nerve function recovery. Knowing that the brain neural stem cells are in proximity with pericytes, the authors speculated whether there existed a CO-induced mutual relationship between neural stem cells and pericytes that promoted nerve regeneration. They first cultured pericytes under a condition deprived of oxygen and glucose and then used CORM-3-treated medium to treat nerve stem cells. They found that such treatment could promote them to differentiate into mature neurons, indicating that CO has the therapeutic effect on brain trauma by protecting vascular pericytes, which interact with neural stem cells to promote nerve regeneration.

The highlight of the study by Eng H Lo group is that this neural protective effect is the result of the interaction

between pericytes and neural stem cells rather than the result of any single cell type. More recently, Eng H Lo group, working with the Capital Medical University in China, published a research paper on *Nature*, reporting that mitochondria from astrocytes could protect neurons after cerebral ischemia.<sup>26</sup> The mode of this research is similar to that used in the research about release of mitochondria from glial cells to save neurons. In other words, they have shifted their research attention from a single cell type to multiple cell types. It is possible to use the same research strategy to explore the way of affecting neurons by releasing damaging or protective molecules from microglial cells.<sup>27</sup>

To sum up, CO plays a positive role in the treatment of TBI, and further study on the understanding of the mechanism about the CO protecting TBI is necessary, through the constant exploration in the future. So, CO owns the great potential application value on new drug development in the treatment of TBI. However, we find that CO and hydrogen have many overlapping effects, based on our previous findings about hydrogen. The key role of CO is its ability to bind hemoglobin and block the combination of oxygen and hemoglobin, which is known as the antioxidant effect. As a matter of fact, oxygen is an injurious factor in the presence of cell function deficiency. One of the effects of CO is to block the toxic effect of oxygen. Although hydrogen can also play the same role against oxygen toxicity, its effect level is by far lower than that of CO. Therefore, hydrogen cannot play the same role as CO unless there is a substantial increase in the dose of hydrogen. If this is possible, research on hydrogen can be conducted with particular reference to the research mode of CO. In addition, an animal study from Wardlaw et al.<sup>28</sup> revealed that H<sub>2</sub> provides nerve protection against transient middle cerebral artery occlusion in rats. This means that the hydrogen can be used as a new therapeutic approach for TBI.

#### Author contributions

LQ and NZ wrote the paper; JLH gave the suggestions; XQY revised the language. All authors read and approved the final manuscript for publication.

#### Conflicts of interest

The authors declare that they have no competing interests.

#### Plagiarism check

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