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LETTER TO THE EDITOR

Carbon dioxide redox metabolites in oxidative eustress and oxidative distress

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Abstract

High carbon dioxide tensions (hypercapnia) are toxic to mammals by both pH-dependent and pH-independent mechanisms that remain partially understood. Relevantly, carbon dioxide reacts with biologically ubiquitous oxygen metabolites such as peroxynitrite and hydrogen peroxide to produce carbonate radical and peroxymonocarbonate, respectively. These metabolites are redox active making it timely to discuss the potential role of carbon dioxide redox metabolites in oxidative eustress and oxidative distress conditions.

Life adaptation to molecular oxygen allowed evolution of complex life forms but came with a cost because oxygen is prone to one-electron transfers, producing radical and oxidant metabolites that are toxic to cells. To cope with these metabolites during evolution, aerobic organisms developed antioxidant defenses (enzymatic and not) and learned to use radicals and oxidants in processes essential to them. Although oxygen and its metabolites imprinted the evolution of complex life forms, the cell damaging mechanisms of these metabolites received most of the attention up to the 1990s. More recently, the participation of radicals and oxidants in both physiological and pathological processes became consensual, and the classical concepts of homeostasis and oxidative stress are being replaced by oxidative eustress and oxidative distress, respectively (Sies and Jones 2020).

In this context, it is timely to discuss the potential role of carbon dioxide (CO_2) redox metabolites in oxidative eustress and oxidative distress conditions. CO_2 levels are increasing in the atmosphere and inside modern refrigerated buildings. This gas is a normal constituent of the human body that produces about 1 kg of CO_2/day through respiration and relies in the CO_2/HCO_3^- pair (bicarbonate buffer) as the main physiological buffer. High CO_2 tensions (hypercapnia) are toxic to mammals by both pH-dependent and pH-independent mechanisms that remain partially understood. Relevantly, CO_2 reacts with biologically ubiquitous oxygen metabolites such as peroxynitrite ($ONOOH/ONOO^-$) (Ferrer-Sueta et al. 2018) and hydrogen peroxide (H_2O_2) (Bakhmutova-Albert et al. 2010) to produce carbonate radical ($CO_3^{\bullet-}$) and peroxymonocarbonate (HCO_4^-), respectively. These metabolites are redox active. The $CO_3^{\bullet-}$ is a strong one-electron oxidant that oxidizes biomolecules to radicals likely resulting in oxidative damage (Augusto and Miyamoto 2012). In contrast, HCO_4^- is a two-electron oxidant more reactive than H_2O_2 towards thiol proteins and may be involved in cellular signaling (Truzzi and Augusto 2018). In the presence of transition metal ions, HCO_4^- produces the $CO_3^{\bullet-}$.

Several lines of evidence indicate the participation of $CO_3^{\bullet-}$ in situations of oxidative damage and distress associated with nitric oxide overproduction (Ferrer-Sueta et al. 2018), hypercapnia (Dean 2010), and related clinical conditions. Conversely, HCO_4^- received limited attention in the literature. Nevertheless, its formation explains the accelerating effects of the CO_2/HCO_3^- pair on H_2O_2-mediated oxidation of thiol proteins that are confirmed players in cellular redox signaling, such as protein tyrosine phosphatases (Zhou et al. 2011) and 2-Cys peroxiredoxins (Truzzi et al. 2019; Peskin et al. 2019). Additionally, the requirement of HCO_3^- for protein-tyrosine phosphatase 1B oxidation and cellular signaling through epidermal growth factor-triggered phosphorylation cascades in adenocarcinoma cells was attributed to HCO_4^- formation (Dagnell et al. 2019). These recent studies support a role for HCO_4^- in H_2O_2-mediated cellular signaling.

The accumulated knowledge on CO_2 redox metabolites, taken together with the estimated ranges of H_2O_2

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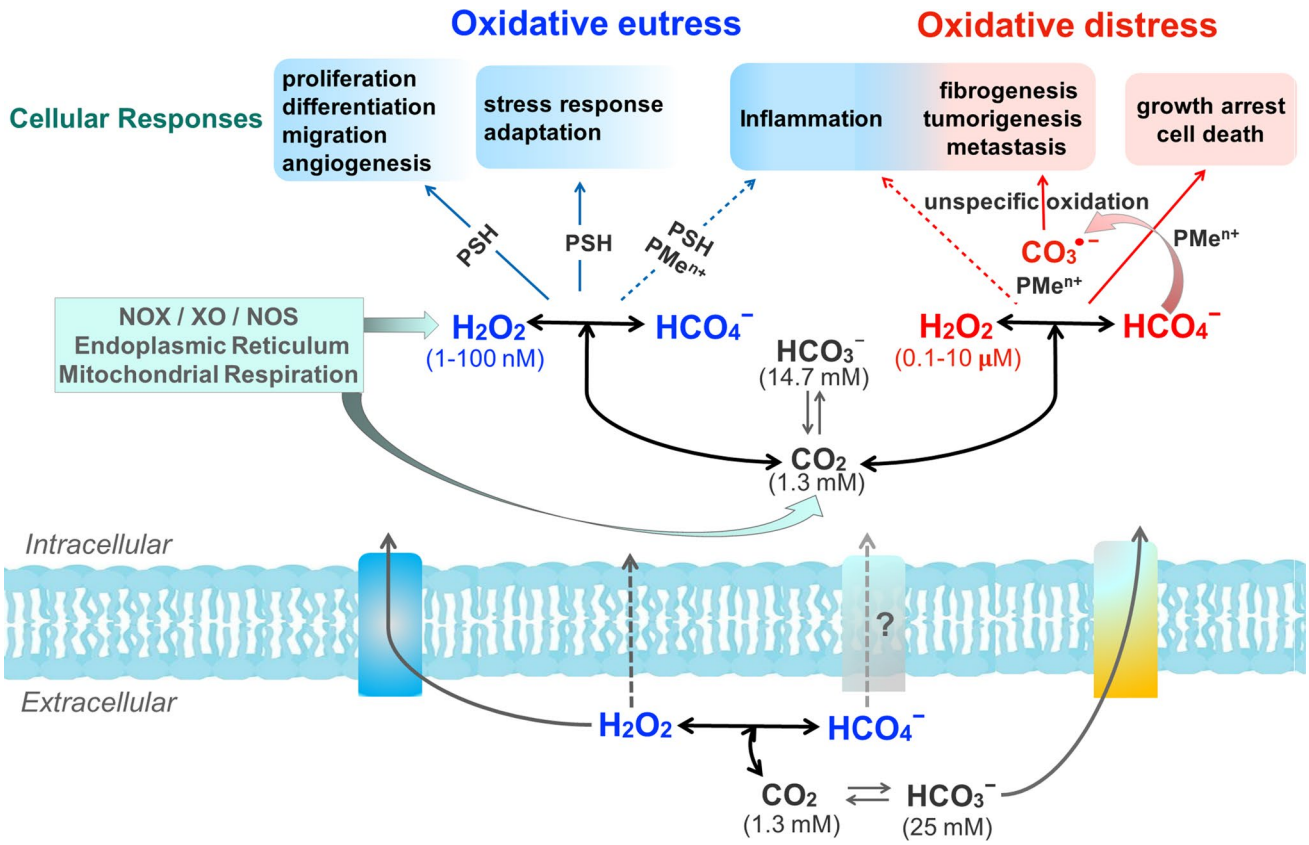

Fig.1 Potential effects of CO_2 redox metabolites (HCO_4^- and $CO_3^{\bullet-}$) on physiological and pathological responses mediated by H_2O_2 and associated with oxidative eustress and oxidative distress conditions, respectively. The used ranges of H_2O_2 concentration physiological (blue) and supraphysiological (red) were those from Sies and Jones, 2020. Based on the estimated value of the K (0.33 M^{-1}) of the equilibrium H_2O_2 plus HCO_3^- with HCO_4^-, the range of HCO_4^- concentration corresponds to approximately 1% of the H_2O_2 range (Bakhmutova-Albert et al. 2010). CO_2 is membrane permeable, H_2O_2 has limited permeability to membranes, but its transport is facilitated by aquaporins, and HCO_3^- can be exchanged by Cl^- through electroneutral Na^+ and HCO_3^- cotransporters; nothing is known about HCO_4^- exchange. The reactions are not balanced. NOX, XO, NOS, PSH, and PMe^{n+} represent NAPDH oxidase, xanthine oxidase, nitric oxide synthase, a generic thiol protein, and a generic protein containing metal center, respectively

concentration associated with different cellular responses (Sies and Jones 2020), permit hypothesizing the influence of HCO_4^- and $CO_3^{\bullet-}$ on them (Fig. 1). The first likely increases H_2O_2-mediated physiological responses whereas the $CO_3^{\bullet-}$ likely increases the pathophysiological ones.

Most of these hypothetical increases remain to be experimentally, proved but the scenario displayed in Fig. 1 emphasizes the likely relevance of CO_2 redox metabolites in health and disease.

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Declarations

Conflict of interest The authors declare no competing interests.

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