MECHANISMS AND PATHOPHYSIOLOGICAL CONSEQUENCES OF REDOX PROCESS. EMPHASIS IN PROCESSES MEDIATED BY BICARBONATE BUFFER, SUPEROXIDE DISMUTASE1, THIOL PROTEINS AND NITROXIDES

Ohara AUGUSTO

Chemistry Institute / University of São Paulo (USP)

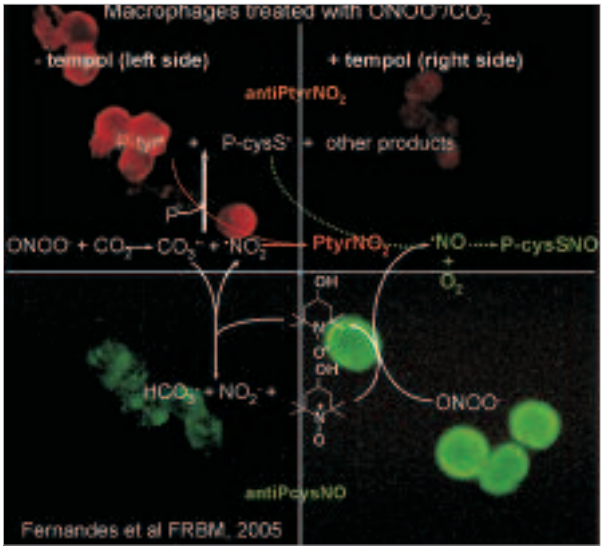

Diagram of the mechanism by which tempol nitroxide drives the reactivity of perixintrito/CO^2 from nitration to nitrosilation of proteins. (from Fernandes et al. 2005. Free Racic. Biol. Med. 38:189)

Currently, free radicals and oxidants are considered to mediate responses that range from signaling circuits involved in physiology and pathology to cellular and tissue injury. It is widely conceded that the elucidation of these many inter-related processes requires a better understanding of cellular oxidative mechanisms, including the identification of involved oxidants, the pathways regulating their generation and their targets at molecular level. In this context, we aim to continue to contribute to the elucidation of the molecular mechanisms and the pathophysiological consequences of redox processes by addressing questions that are timely and relevant to the human health.

Thus, the sources and fates of oxidants derived from bicarbonate buffer will be examined. We contributed to demonstrate that bicarbonate buffer modulates redox processes and are convinced that recognition of the oxidants derived from it will provide new perspectives to the understanding and control of numerous pathophysiological states and clinical conditions such as emhysema, respiratory muscle paralysis and pulmonary fibrosis. Also, we aim to advance in understanding structural and mechanistic aspects that modulate the pro-oxidant activities of the enzyme superoxide dismutase1. It is expected that these studies will contribute to the elucidation of neurodegenerative processes, in particular those associated with amyotrophic lateral sclerosis. In addition, we will continue to study the thiol proteins as controllers and sensors of biological oxidants because these proteins have only recently been recognized as players in redox processes and our previous kinetic and mechanistic studies provided insights about their multiple physiological roles. Finally, we will continue to study the mechanisms by which the nitroxide tempol is protective against oxidative and nitrosoactive conditions in vitro and in experimental animals. In our view these studies are relevant because nitroxides may constitute new antioxidant therapies, including to presently untreatable diseases such as multiple sclerosis and amyotrophic lateral sclerosis.

SUMMARY OF RESULTS TO DATE AND PERSPECTIVES

Our project aimed to contribute to the understanding of two general problems: (i) the biochemistry of oxidants derived from nitric oxide, such as peroxynitrite, nitrogen dioxide and carbonate radicals; and (ii) the mechanism and protection of tissue injury in inflammatory/infectious conditions by urate and nitroxides. I consider that the project developed well, although not all of the studies were finalized and published, in particular those involving animal models. In addition, as it is usual in scientific endeavors, some of the initial goals were redirected as a consequence of new insights obtained by us and other investigators during the project. Here, we report the main conclusions and perspectives of the project, limiting the references to our own work.

In regard to the biochemistry of nitric oxide-derived oxidants, we contributed particularly to the understanding of the physiological sources and fates of the carbonate radical. These studies led us to reveal other oxidants derived from the bicarbonate buffer, such as peroxymonocarbonate which was suggested to participate in the bicarbonate-dependent peroxidase activity of the enzyme superoxide dismutase1. We are convinced that recognition of oxidants derived from the main physiological buffer will provide new mechanistic insights into the understanding and control of numerous pathological processes and clinical conditions, such as emphysema, respiratory muscle paralysis and pulmonary fibrosis. Thus, these studies will be further pursued. In addition, we speculated that production of the carbonate radical during the peroxidase activity of superoxide dismutase1 promotes enzyme dimerization/aggregation as an important event leading to motor neuron degeneration in amyotrophic lateral sclerosis (ALS). In the next project, we aim to advance the understanding of the structural and mechanistic factors which modulate the pro-oxidant activities of superoxide dismutase1. In a previous study, we also advanced the comprehension of the mechanisms by which nitroxides inhibit tissue injury associated with conditions of oxidative and nitro-oxidative stress *in vitro* and *in vivo*. The potential of nitroxides as new therapeutic strategies makes it relevant to deepen these mechanistic studies and to examine tempol efficiency in protecting animal models animals of neurodegenerative processes, such as those associated with multiple sclerosis and amyotrophic lateral sclerosis. In parallel, it will be important to develop and test novel cyclic nitroxides as proposed in the current study. Finally, we should mention our recent studies which provided new perspectives to the understanding of peroxiredoxins as sensors and controllers of biological oxidants.

MAIN PUBLICATIONS

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Ohara AUGUSTO

Instituto de Química
Universidade de São Paulo (USP)
Caixa Postal 26077 – Cidade Universitária
05513-970 – São Paulo, SP – Brasil

+55-11-3091-3873
oaugusto@iq.usp.br