Differential clinical impacts of oxidative stress and nitrosative stress: Therapeutic implications

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The central theme of this lecture is that oxidative stress and nitrosative stress bear differential clinical impact, and that therapeutic intervention is only achievable against pathophysiological, but not pathological conditions. Using as the illustrative example is baroreflex dysregulation, which by itself is not a disease per se, although it impacts daily existence of the general populace and in its most severe form is causally related to fatality. Under physiological conditions, the baroreflex provides a rapid negative feedback mechanism that normalizes fluctuations in blood pressure and heart rate induced by environmental insults. Under pathophysiological conditions such as neurogenic hypertension, the baroreflex is rendered dysfunctional because of oxidative stress in its brain stem neural substrates. More importantly, this process is reversible and antioxidant treatment is attainable. When baroreflex is defunct under pathological conditions, nitrosative stress in key nuclei of the baroreflex circuit becomes the primary culprit, which leads to brain dead and other forms of fatality. Intriguingly, this process is irreversible, with diminished therapeutic feasibility. Previous and ongoing work from our group has unveiled an intricate interplay of a multitude of signaling molecules at the level of transcription, translation and post-translational modification in its brain stem neural substrates dictates the phenotypical expression of normal, dysfunctional or defunct baroreflex; and reversible or irreversible disruption of the functional connectivity between key nuclei of the baroreflex circuit determines its pathophysiological or pathological status. Representative examples from our clinical and laboratory work will be used to illustrate these views, including some obtained from recent studies using magnetic resonance imaging/diffusion tensor imaging as an investigative tool in mouse disease models. We conclude that the transition from oxidative stress to nitrosative stress bears crucial clinical impacts on baroreflex dysregulation, and interruption of the associated transition from pathophysiology to pathology should be regarded as a pivotal therapeutic target.

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