ABSTRACT

Mini Symposia

MS2D-1-1 Regulation of neuronal function by S-nitrosylation and oxidation

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Oxidative stress is thought to be a general contributing factor to ageing. Actually, various correlations between age and the accumulation of the oxidative damage to cellular macromolecules, such as proteins, have been demonstrated. However, how oxidative stress affects brain function is not fully understood. Recently, we identified long-term potentiation (LTP) at cerebellar synapses. The LTP is dependent on S-nitrosylation of cerebellar proteins by NO (NO-LTP). Because cysteine is a target of S-nitrosylation by NO as well as a target of oxidative signals, we examined whether NO-LTP is affected by oxidizing signals: NO-LTP as well as S-nitrosylation of cerebellar proteins were inhibited by oxidative reagents (i.g. H_2O_2). These results suggested that oxidizing signal impaired NO-LTP through inhibition of S-nitrosylation.Very recently, we identified novel Ca^{2+}-releasing mechanisms, NO-induced Ca^{2+} release (NICR). NICR is mediated by a type of Ca^{2+} release channel, type 1 ryanodine receptor (RyR1), and dependent on S-nitrosylation of RyR1. Because NICR is essential for the induction of NO-LTP, it is highly possible that NICR is inhibited by oxidative signals. Effects of oxidative signals on NICR as well as S-nitrosylation of RyR1 will be introduced in this symposium.

MS2D-1-2 A potential therapeutic approach for heart failure: Water-soluble N-nitrosamines inducing S-nitrosylaton without NO release target desensitization of βadrenergic receptor

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Desensitization of ßadrenergic receptors (ßARs) underlies the pathogenesis of heart failure and resistance to ßagonists. In the regulation of ßAR signaling, G protein-coupled receptor kinase 2 (GRK2) may be a potential therapeutic target because GRK2 plays an essential role in ßAR desensitization. Although it has been shown that S-nitrosylation of GRK2 inhibits GRK2 activity, a potential problem is that compounds that induce S-nitrosylation also generate NO, which itself operates for cardiovascular protection. In our study, we have successfully developed water-soluble compounds that induce nitrosylation but do not generate NO. Our compounds at least partly, rescue ßAR from desensitization in HEK 293 cells and in rat cardiac myocytes. They inhibit isoproterenol-dependent phosphorylation and internalization of ß2AR. Indeed, they nitrosylate GRK2 in vitro and in cells, and their S-nitrosylation of GRK2 likely underlies their inhibition of ß2AR desensitization. Our compounds that induce S-nitrosylation without NO release may serve as useful biological tools for future studies and potential therapeutics for clinical application.

MS2D-1-3 Application of molecular hydrogen on Parkinson's disease and neuromuscular disorders

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Therapeutic effects of molecular hydrogen have been investigated since 2007. More than 230 original articles have been published since 2007. The effects have been reported in essentially all organs covering 29 disease categories that can be subdivided into 138 human diseases with a predominance of oxidative stress-mediated diseases and inflammatory diseases.

We here present a marked effect of molecular hydrogen on a rat model of PD. A similar effect has been reported in an MPTP-induced mouse model of PD. Furthermore, a randomized double-blind placebo-controlled trial revealed that hydrogen water improves total UPDRS scores in PD patients. A large amount of hydrogen is produced by intestinal microbes and we present that that breath hydrogen concentrations in PD patients are lower than those in healthy controls. An analysis of intestinal microbiota in PD patients will be also presented.

We propose that lowered production of molecular hydrogen by intestinal microbes in PD patients partly accounts for the development and progression of PD. We also propose that molecular hydrogen is protective against PD, although the underlying mechanisms of the marked effects of molecular hydrogen still remain elusive.

MS2D-1-4 H_2 (hydrogen) gas can be used as a brain resuscitation gas

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Despite advances in the management of patients who experience a nontraumatic cardiac arrest (CA), survival rates remain low, and many survivors are left with neurological and cardiac sequelae. Post-CA syndrome, including neurological dysfunction, cardiac damage, and sepsis-like systemic inflammation, is likely to contribute to the multisystem organ dysfunction and ultimate demise of many CA victims. Therapeutic hypothermia is widely accepted as the gold standard method to improve survival and to limit neurological outcomes in patients who achieve return of spontaneous circulation after CA. However, it is still underused, and there is a need for the development of alternative approaches to ameliorate the prognosis of post-CA patients. Hydrogen gas (H2) has antioxidant and anti-inflammatory properties, and its protective effects have been demonstrated in different animal models. We showed that H2 inhalation, begun after resuscitation with normoxia, improves neurological outcome in a rat model of CA independently of targeted temperature management. Histological studies confirmed that improved neurological outcomes were associated with reduced neuronal degeneration and microglial activation in a selectively vulnerable brain region.