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Age-dependent action of reactive oxygen species on transmitter release in mammalian neuromuscular junctions

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ABSTRACT

Reactive oxygen species (ROS) are implicated in aging, but the neurobiological mechanisms of ROS action are not fully understood. Using electrophysiological techniques and biochemical assays, we studied the age-dependent effect of hydrogen peroxide (H_2O_2) on acetylcholine release in rat diaphragm neuromuscular junctions. H_2O_2 significantly inhibited both spontaneous (measured as frequency of miniature end-plate potentials) and evoked (amplitude of end-plate potentials) transmitter release in adult rats. The inhibitory effect of H_2O_2 was much stronger in old rats, whereas in newborns tested during the first postnatal week, H_2O_2 did not affect spontaneous release from nerve endings and potentiated end-plate potentials. Proteinkinase C activation or intracellular Ca^{2+} elevation restored redox sensitivity of miniature end-plate potentials in newborns. The resistance of neonates to H_2O_2 inhibition was associated with higher catalase and glutathione peroxidase activities in skeletal muscle. In contrast, the activities of these enzymes were downregulated in old rats. Our data indicate that the vulnerability of transmitter release to oxidative damage strongly correlates with aging and might be used as an early indicator of senescence.

1. Introduction

It has been well documented that in physiological state, reactive oxygen species (ROS) play a key role in physiological cell signaling, but increased level of ROS production (and/or decreased antioxidant and repair systems activity) leading to increased oxidative stress are implicated in the development of different pathologies (Droge, 2002; Rhee, 2006; Sena and Chandel, 2012). The nervous system is highly vulnerable to oxidative stress and redox imbalance, which contributes to neuronal apoptosis and cognitive decline resulting in a number of neurodegenerative disorders including Parkinson's disease (Sanders and Timothy Greenamyre, 2013; Zuo and Motherwell, 2013), Alzheimer's disease (Jomova et al., 2010; Yan et al., 2013), and amyotrophic lateral sclerosis (ALS; D'Amico et al., 2013; Naumenko et al., 2011; Shi et al., 2010). Aging is associated with increased oxidative damage and failure of antioxidant defense, which result in higher incidence of a wide range of the oxidative stress-induced neurodegenerative processes (Balaban et al., 2005; Jackson and McArdle, 2011; Radak et al., 2013; Salminen and Paul, 2014). Nevertheless, there is limited information on the impact of ROS on the function of synapses, key elements of the nervous system. In particular, there are no studies which address the developmental aspect of ROS action on synaptic transmission. We have shown earlier that hydrogen peroxide (H_2O_2) caused a strong inhibition of synaptic transmission in adult mice. This effect was likely mediated by synaptosomal-associated protein 25, one of the presynaptic soluble N-ethylmaleimide-sensitive factor activating protein receptor proteins (Giniatullin et al., 2006). The neuromuscular junction is a classical model to study synaptic processes, performing reliable recordings from young, adult, and old animals. In the present study, we investigated the action of ROS on synaptic transmission at different stages of life

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