PARKINSON'S DISEASE, RESPIRATION, AND N-OLEOYL-DOPAMINE: PRELIMINARY OBSERVATIONS AND HYPOTHESIS

Monika Bialkowska, Dominika Zajac, and Mieczyslaw Pokorski

Department of Respiratory Research, Medical Research Center, Polish Academy of Sciences, Warsaw, Poland

Parkinson's Disease (PD) is indisputably linked with central dopamine (DA) insufficiency. Depressed lung ventilation in PD is highly prevalent, difficult to manage, and has an obvious negative impact on quality of life and morbidity due to developing hypoxia. The underlying mechanisms of depressed breathing in PD are unclear. They may be mechanical, due to the head-flexed posture or rigidity of the respiratory muscle pump, or functional, due to reduced DA brain content. The role of DA disturbance in the carotid body, an organ that generates the hypoxic ventilatory response, in ventilator insufficiency in PD has not yet been explored. DA supplementation cannot be used in PD studies due to DA fleeting effects and the inability to penetrate the blood-brain-barrier. Recently, we have developed a novel lipid derivative of DA, N-oleoyl-dopamine (OLDA), being a condensation product of DA and oleic acid. In a series of experimental studies, we have found that OLDA penetrates into the brain neural membranes after systemic injection and stays there as a stable compound. Thus, OLDA has the potential to become a prodrug for dopamine delivery into the brain in PD. Indeed, OLDA displays some properties which may help relieve Parkinsonian symptoms. These include increased motor activity or diminished muscle rigidity in a reserpine model of rat PD, both involving a DA pathway. We have also found, however, that OLDA, acting in DA-like manner, inhibits ventilation and its responses to hypoxia, which can hamper its usefulness in PD. In the ongoing research we have put forward a hypothesis that the inhibitory effect on ventilation of OLDA in the healthy condition may not necessarily correspond with the Parkinsonian condition. Enhanced brain DA activity carried over by OLDA may actually increase hypoxic ventilatory reactivity by overriding the carotid body-mediated DA-linked depressant effects on ventilation. OLDA could then ameliorate the respiratory sequela of PD. The resolution of this issue would require study designs which would take into consideration the effects of chronic PD on the morphology and function of the carotid body and the separation of central and peripheral ventilatory actions of OLDA.