Peran Protein *Hypoxia Inducible Factor-1α* (HIF-1α) Terhadap Regulasi Ekspresi Gen *Manganese-Superoxide Dismutase* (MnSOD) pada Induksi Hipoksia Sistemik

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Hypoxia is a pathological condition in which the body as a whole or region of the body (tissue or cell) deprived of adequate oxygen supply. The transcriptional regulator hypoxia inducible factor-1 (HIF-1) is an essential mediator of O_2 homeostasis. Unlike the β subunit (HIF-1β), the activity of HIF-1α is controlled in an oxygen-dependent manner. The stability and expression of HIF-1α during hypoxia is remarkably higher than those under normoxic conditions. During hypoxia, the production of reactive oxygen species (ROS), such as superoxide anion, is enhanced.

Manganese superoxide dismutase (MnSOD), as a major endogenous antioxidant enzyme in mitochondrial matrix, could convert superoxide radicals to hydrogen peroxide, hence prevents the cell oxidative damage. Our hypothesis is that HIF-1α is involved in the regulation of MnSOD gene expression during hypoxia. Goals of this study were to determine whether the mRNA expression and the activity of MnSOD in brain, heart and leucocyte cells are affected by the expression of mRNA HIF-1α under induced systemic hypoxic condition of adult rats. Twenty-five male Sprague Dawley rats were subjected to systemic hypoxia by placing them in the hypoxic chamber supplied by 10% of O_2 for 0, 1, 7, 14 and 21 days, respectively.

The relative expression level of HIF-1α and MnSOD mRNA in brain, heart and leucocyte cells were analyzed using quantitative RT-PCR assay based on Pfaff's formula. The MnSOD enzyme specific activity was biochemically determined using RanSOD® kit. This study demonstrates that the relative expression level of HIF-1α was gradually increased up to 7 days of hypoxia induction in heart and brain, and was slightly decreased after 7 days suggesting that the responsive pathways for adaptation have been sufficiently expressed in both tissues. In contrast to that data, in leucocyte cell the stimulation of HIF-1α expression was intensively maintained up to 21 days although the expression has reached the remarkably high level. This indicates that the leucocyte cells require more adaptive changes induced by HIF-1α to enhance O_2 uptake and distribution.

The relative expression level of MnSOD mRNA in heart, brain and leucocyte cells was also increased during hypoxia induction, although it was not parallel to the increase of HIF-1α expression level. This result suggests that HIF-1α did not directly regulate the expression of MnSOD or the stimulation of MnSOD expression during hypoxia was

regulated through other pathway than that induced by HIF-1α. Furthermore, the specific activity of MnSOD was gradually increased up to 14 days, however after 14 days it had a tendency to decrease showing that under chronic hypoxic condition the capacity of MnSOD to eliminate the accumulated ROS has been saturated. Taken together all the data, we could conclude that the MnSOD gene expression during hypoxia was not regulated by HIF-1α protein and the oxygen sensing in brain, heart and blood tissue have different capacity and sensitivity, due to the importance of oxygen homeostasis in the tissue. Further studies are required to analyzed the expression of MnSOD in other tissues, as well as to analyzed the correlation of MnSOD expression with the cell apoptosis during hypoxia.