

Perubahan ekspresi gen dan aktivitas spesifik karbamoil fosfat sintetase 1 dan protein hif 1 pada hati tikus *Rattus norvegicus* sebagai adaptasi terhadap hipoksia sistemik kronik = The changeover of gene expression and specific activity of carbamoyl phosphate synthetase 1 cps 1 and hif 1 protein of rat *Rattus norvegicus* liver during systemic chronic hypoxia

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Abstrak

Tujuan: Tujuan penelitian ini adalah untuk mempelajari perubahan ekspresi dan aktivitas spesifik karbamoil fosfat sintetase 1 (Carbamoyl Phosphate Synthetase 1/CPS 1) dan protein HIF-1 (hypoxia-inducible factor) pada hati tikus (*Rattus norvegicus*) selama hipoksia sistemik kronik.

Disain: Disain penelitian ini adalah eksperimen *in vivo* dengan menggunakan tikus sebagai hewan coba.

Metode: Ada lima perlakuan tikus; tikus kontrol, hipoksia 1 hari, hipoksia 3 hari, hipoksia 5 hari dan hipoksia 7 hari. Ekspresi gen karbamoil fosfat sintetase 1 (CPS1) diukur menggunakan real time RT-PCR dan menggunakan 18s rRNA sebagai gen referensi. Aktivitas spesifik CPS1 diukur menggunakan hidroksiurea sebagai larutan standar. Metode ELISA digunakan untuk mengukur protein HIF-1.

Hasil : Ekspresi gen karbamoil Fosfat Sintetase 1 meningkat secara signifikan dan menunjukkan ekspresi tertinggi daripada perlakuan lain pada satu hari hipoksia dibandingkan dengan kelompok control. Pada hipoksia hari berikutnya, ekspresi CPS1 menurun secara signifikan dibandingkan kelompok control (ANOVA, $p < 0,05$). Aktivitas spesifik CPS1 meningkat secara signifikan pada satu hari dan tiga hari hipoksia dibanding kelompok control (ANOVA, $p < 0,05$). Protein HIF-1 juga dipengaruhi oleh induksi hipoksia (ANOVA, $p < 0,05$). Hubungan antara ekspresi dan aktivitas CPS1 menunjukkan hubungan positif kuat dan hubungan protein HIF-1 dan ekspresi CPS1 menunjukkan hubungan positif sedang (Pearson, $p < 0,05$). Sedangkan hubungan antara protein HIF-1 dan aktifitas spesifik menunjukkan tidak ada hubungan secara statistik.

Kesimpulan: Kondisi hipoksia berperan penting dalam pengaturan ekspresi gen dan aktivitas spesifik CPS1 serta protein HIF-1. Regulasi ekspresi gen CPS1 oleh HIF-1 belum diketahui.

Background: The aim of this research is to study the changeover of expression and specific activity of Carbamoyl Phosphate Synthetase 1 (CPS 1) and HIF-1 protein of rat (*Rattus norvegicus*) liver during systemic chronic hypoxia.

Design: Design of this research is an *in vivo* experimental study using rat as laboratory animal.

Method: There are five treatment of rats; control, 1 day of hypoxia, 3 days of hypoxia, 5 days of hypoxia and 7 days of hypoxia. Carbamoyl phosphate synthetase 1 gene expression was measured using real time RT-PCR and using 18s RNA gene as housekeeping gene. The specific activity of CPS1 was measured using hydroxyurea as standard solution. ELISA was performing in order to measure HIF-1 protein.

Result: Carbamoyl phosphate synthetase 1 gene expression was increased significantly and shows the highest expression than other treatment in one day of systemic chronic hypoxia treatment of rat liver compared with control group. And the following days of hypoxia CPS1 gene expression were decreased significantly than control group (ANOVA, $p < 0,05$). The specific activity of CPS1 was increased significantly in one day and three days of systemic chronic hypoxia than control group (ANOVA, $p < 0,05$).

The HIF-1 protein was decreased in one day and increased in three days of systemic chronic hypoxia than control group (ANOVA, $p < 0,05$). The correlation between expression and specific activity of CPS1 shows strong positive correlation and between HIF-1 protein and CPS1 expression shows moderate positive correlation (Pearson, $p < 0,05$). The HIF-1 protein and specific activity of CPS1 shows no correlation statistically.

Conclusion: Hypoxic condition plays an important role in the regulation of gene expression and specific activity of CPS1 and HIF-1 protein. Regulation of CPS1 gene expression by HIF-1 is not known yet.