Efek magnesium terhadap perubahan konsentrasi kalsium intraselular akibat halotan penelitian in vitro pada sel kultur kardiomiosit tikus = The effect of magnesium on halothane induced intracellular calcium concentration changes in cardiomyocytes

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Abstrak

Latar belakang: Halotan, anestetika inhalasi yang poten semakin banyak ditinggalkan karena efek aritmogeniknya. Penelitian di tingkat selular kebanyakan dilakukan pada penyandang hipertermia maligna (MH), membuktikan bahwa halotan mengaktivasi reseptor ryanodin (RyR) pada otot rangka, menyebabkan penglepasan berlebihan Ca2+ dari retikulum sarkoplasmik (SR) ke sitosol, memicu hiperkontraktur otot rangka. Diasumsikan halotan mempunyai efek serupa pada otot jantung. Belum banyak penelitian mengenai efek pemberian Mg2+ terhadap perubahan konsentrasi Ca2+ akibat halotan, meskipun Mg2+ dikenal sebagai obat antiaritmik. Mg2+ diduga menurunkan konsentrasi Ca2+ sitosol dengan cara meningkatkan ambilan kembali ke dalam SR melalui aktivitas SERCA.
Metode penelitian: Penelitian ini adalah penelitian eksperimental in vitro, dengan subjek sel kultur miosit jantung tikus. Miosit yang dimuat dengan indikator Indo1 dibagi menjadi lima kelompok. Sel kontrol tidak dipajankan dengan halotan. Kelompok sel lainnya dipajankan dengan halotan berkonsentrasi 2 mM (setara dengan 1 - 3 MAC) selama 5 menit. Pada kelompok 1, setelah dipajankan dengan halotan, pajanan dihentikan dan diperiksa besar emisinya (penghentian menit ke- 0). Selanjutnya pemeriksaan emisi dilakukan setelah penghentian pajanan diteruskan selama 5, 10, 15 dan 20 menit. Sel kelompok 2 dan 3 diberi MgSO4 11 M dan 22 mM setelah pajanan halotan, kelompok 4 dan 5 diberi MgSO4 11 mM dan 22 mM sebelum pajanan halotan. Perubahan konsentrasi Ca2+ sitosol diketahui dengan pemindaian laser menggunakan mikroskop konfokal, dihitung dari perubahan besar emisi pada sel terpajan dengan analisis pixel.
Hasil: Halotan meningkatkan konsentrasi Ca2+ sitosol jantung secara bermakna. Pemberian MgSO4 sebelum pajanan halotan tidak mencegah peningkatan konsentrasi Ca2+ sitosol. Pemberian MgSO4 setelah pajanan halotan tidak bermakna menurunkan konsentrasi Ca2+ sitosol, namun ditemukan kecenderungan turunnya konsentrasi Ca2+ sitosol dengan penambahan dosis MgSO4, setara dengan efek penghentian pajanan halotan selama 10 menit. Lima belas menit setelah penghentian pajanan halotan, konsentrasi Ca2+ turun secara bermakna. Dua puluh menit setelah pajanan halotan dihentikan, konsentrasi Ca2+ sitosol telah kembali ke nilai awal.
Simpulan: Halotan meningkatkan konsentrasi Ca2+ sitosol jantung. Mg2+ tidak bermakna menurunkan konsentrasi Ca2+ sitosol jantung dan tidak mencegah peningkatan konsentrasi Ca2+ sitosol jantung akibat pajanan halotan. Setelah penghentian pajanan halotan selama 15 menit, konsentrasi Ca2+ sitosol turun secara bermakna.
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Background: Halothane, a potent inhalational anesthetic, has been recognized to cause arrhythmia, probably due to activation of ryanodine receptor (RyR), triggering Ca2+ release from sarcoplasmic reticulum (SR) to the cytosol. The similar mechanism had been known in skeletal muscle of malignant hyperthermia (MH)

patients. Mg^{2+} hypothetically prevents Ca^{2+} release by inhibition of RyR and increasing Ca^{2+} reuptake to SR by SERCA activity. Although Mg^{2+} had been used as an antiarrhythmic agent, the effect on reducing halothane-induced high intracellular Ca^{2+} concentration is not well studied.
Method: This experimental in vitro study was done on cultured cell of rat cardiomyocytes. Cells divided into 6 groups. 5 groups were exposed to halothane for 5 minutes (at concentration of 2 mM, equal to 1-3 MAC) and one was not. Of the 5 halothane-exposed groups, group 1 received no additional treatment, but observed immediately after discontinuation of halothane exposure, then 5, 10, 15 and 20 minutes after discontinuation. Group 2 and 3 were given 11 mM and 22 mM $MgSO_4$ after halothane exposure, respectively. Group 4 and 5 had the corresponding $MgSO_4$ treatment prior to exposure. The change in cytosolic Ca^{2+} was observed by a confocal microscope and measured by pixel analysis for the emission.
Results: Halothane increased cytosolic Ca^{2+} concentration in rat cardiac myocytes, in which was not substantially altered by $MgSO_4$ given before or after the exposure. There was a trend of decreasing Ca^{2+} concentration with higher dose of Mg^{2+}. $MgSO_4$ of 22 mM decreased cytosolic Ca^{2+} concentration to the same extent as discontinuation of halothane for 10 minutes. The cytosolic Ca^{2+} concentration significantly decreased 15 minutes after discontinuation of halothane exposure and the cytosolic Ca^{2+} concentration returned to the basal level 20 minutes after discontinuation of halothane exposure.
Conclusion: Halothane increases cytosolic Ca^{2+} concentration in rat cardiac myocytes. Neither pre- nor post-halothane exposure administration of $MgSO_4$ substantially alters this phenomenon. Cytosolic Ca^{2+} concentration was significantly reduced 15 minutes after discontinuation of halothane exposure.