Deep thiopental anesthesia alters glucose homeostasis but not the neurochemical profile in rat cortex

H. Lei[1,2], J. M. Duarte[1,2], V. Mlynarik[1], A. Python[1], and R. Gruetter[1,3]

[1]EPFL, Lausanne, Vaud, Switzerland, [2]UNIL, Lausanne, Vaud, Switzerland, [3]UNIGE, Geneva, Geneva, Switzerland

Introduction

Barbiturates are widely used as anesthetics and may suppress brain energy metabolism and inhibit both glucose transport at blood-brain barrier (BBB) and cerebral glucose utilization (CMR_{glc}) (1). However, commercial pentobarbital is normally supplied in alcoholic solutions containing, for example, ethanol and propylene glycol (2), which affect glucose transport and CMR_{glc} in rat cortex (3), and possibly cause osmotic opening the BBB (4). Consequently, results from previous studies using those commercially available pentobarbital might reflect mixing effects of this particular cocktail and thus mask the influence of pentobarbital itself, for example, on the glucose transport kinetics (1). Recent *in vivo* studies using ^{1}H NMR spectroscopy suggested that both ethanol and propylene glycol exhibit visible peaks (2,5) and thus could negatively affect absolute quantification of metabolites, in particular glucose (Glc). Therefore, instead of pentobarbital for deep anesthesia, we investigated the effect of another barbiturate, thiopental on glucose transport kinetics and neurochemical profile in the rat cortex using ^{1}H NMR spectroscopy.

Materials and Methods

Under authorizations of the local veterinary authorities, male Sprague Dawley rats (n=14, 284±45g) were prepared under 2% isoflurane anesthesia in O_2 gas and mechanically ventilated (1). Anesthesia was switched to either α-chloralose (40mg/kg initial bolus and followed by 27mg/kg/hr continuous rate infusion) or thiopental (50mg/kg initial bolus and followed by 80-90mg/kg/hr continuous rate infusion, which induced iso-electricity confirmed by electroencephalogram (EEG, data not shown)). Temperature, $PaCO_2$ and pH were maintained in the physiological range (temperature~38 °C, pH~7.4 and PCO_2~45mmHg). All MR experiments were performed in an actively shielded horizontal 9.4T. After the automatical adjustment of field inhomogeneities with the resulting water linewidth in the range of 13-17Hz, the neurochemical profile could be obtained from rat cortex in a 6.5×1.5×3.5µl volume (TE=2.8 ms, TR=4 sec, nt = 320) using SPECIAL (6). Spectra were quantified using LCModel (7). To evaluate cortex glucose transport kinetics, steady-state glycemia was maintained at least 20 min before NMR measurement by adjusting continuous rate of 20% (w/v) D-glucose solution in response to the concomitant measured plasma glucose. The glucose transport kinetic parameters were estimated using the reversible MM model (ReMM) (8). The neurochemical profile was compared with the two-way ANOVA followed by Bonferroni's post-test.

Results and Discussion

No apparent difference was observed in the spectra (Figure 1A and 1B) or either in the difference of two spectra (Figure 1C). Consequently, nearly identical neurochemical profiles (Figure 1D) were obtained under light α-chloralose and deep thiopental anesthesia. When plotting the steady-state cortex glucose concentrations as function of plasma glucose, elevated glucose levels in cortex were systematically observed under deep thiopental anesthesia (Figure 2). The resulting apparent transport kinetics, $T_{max}/CMR_{glc,}$ was increased by 47% in deep thiopental anesthesia (Table 1) when compared to α-chloralose, which is consistent with the previously observed an increase in deep pentobarbital anesthesia (1). In conclusion, with the successful elimination of alcohols or other potential influents such as N_2O, deep thiopental anesthesia could affect cortex glucose transport kinetics with nearly no effect on other metabolites.

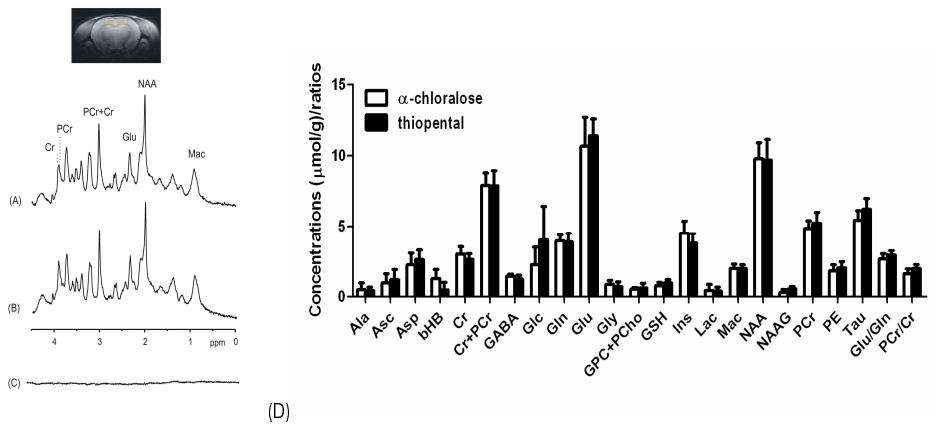

Figure 1. Typical cortex spectra (A and B), the difference (C), and the obtained neurochemical profiles (D) from two anesthesia, light α-chloralose (A) and deep thiopental (B). In order to illustrate difference between two anesthetics with no major glucose contamination, spectra were obtained at two different plasma glucose levels, 33mM for α-chloralose and 24mM for thiopental. Data are shown as mean±SD.

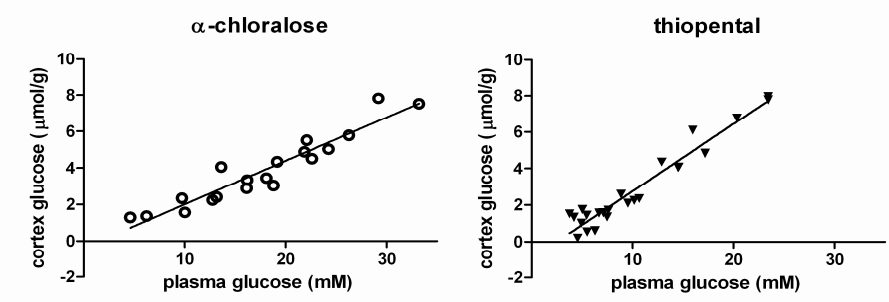

Figure 2. Steady-state cortex glucose content as a function of plasma glucose concentration under α-chloralose (open circles) and deep thiopental (solid triangles) anesthesia. Cortex glucose contents under thiopental anesthesia were apparently higher that those under α-chloralose. Black straight lines represented the fit of ReMM model.

Table 1 Summary of cortex glucose transport kinetics results by the ReMM models.

	α-chloralose	*thiopental*
T_{max}/CMR_{glc}	2.8 ± 0.2	1.9 ± 0.1
K_t (mM)	4.6 ± 1.4	1.4 ± 1.4

Data are shown in mean ± SEs.

References

1. Choi IY et al. J Cereb Blood Flow Metab 2002 22:1343
2. Iltis I et al. Mag Reson Med 2008 59 :631
3. Handa RK et al. Meta Brain Dis 2000 15:211
4. Demey HE et al 1987 Intensive Care Med 14:221
5. Hetherington HP et al. Mag Reson Med 1999 42:1019
6. Mlynarik V et al. Mag Reson Med 2006 56:965
7. Provencher S Mag Reson Med 1993 30:672
8. Choi et al. J Cereb Blood Flow Metab 2001 21:653

Acknowledgements:

Supported by NIH grant R01NS042005, Centre d'Imagerie BioMédicale (CIBM) of the UNIL,UNIGE, HUG, CHUV, EPFL and the Leenaards and Jeantet Foundations