BJA

British Journal of Anaesthesia, 121 (1): 281–290 (2018)

doi: 10.1016/j.bja.2018.04.008
Advance Access Publication Date: 8 May 2018
Research Article

Comparative effects of dexmedetomidine, propofol, sevoflurane, and S-ketamine on regional cerebral glucose metabolism in humans: a positron emission tomography study

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Abstract

Introduction: The highly selective α_2-agonist dexmedetomidine has become a popular sedative for neurointensive care patients. However, earlier studies have raised concern that dexmedetomidine might reduce cerebral blood flow without a concomitant decrease in metabolism. Here, we compared the effects of dexmedetomidine on the regional cerebral metabolic rate of glucose (CMR_{glu}) with three commonly used anaesthetic drugs at equi-sedative doses.
Methods: One hundred and sixty healthy male subjects were randomised to EC_{50} for verbal command of dexmedetomidine (1.5 ng ml^{-1}; n=40), propofol (1.7 μg ml^{-1}; n=40), sevoflurane (0.9% end-tidal; n=40) or S-ketamine (0.75 μg ml^{-1}; n=20) or placebo (n=20). Anaesthetics were administered using target-controlled infusion or vapouriser with end-tidal monitoring. ^{18}F-labelled fluorodeoxyglucose was administered 20 min after commencement of anaesthetic

Editorial decision: December 16, 2017; **Accepted:** December 16, 2017

administration, and high-resolution positron emission tomography with arterial blood activity samples was used to quantify absolute CMR_{glu} for whole brain and 15 brain regions.
Results: At the time of [F^{18}]fluorodeoxyglucose injection, 55% of dexmedetomidine, 45% of propofol, 85% of sevoflurane, 45% of S-ketamine, and 0% of placebo subjects were unresponsive. Whole brain CMR_{glu} was 63%, 71%, 71%, and 96% of placebo in the dexmedetomidine, propofol, sevoflurane, and S-ketamine groups, respectively ($P<0.001$ between the groups). The lowest CMR_{glu} was observed in nearly all brain regions with dexmedetomidine ($P<0.05$ compared with all other groups). With S-ketamine, CMR_{glu} did not differ from placebo.
Conclusions: At equi-sedative doses in humans, potency in reducing CMR_{glu} was dexmedetomidine>propofol>ketamine=placebo. These findings alleviate concerns for dexmedetomidine-induced vasoconstriction and cerebral ischaemia.
Clinical trial registration: NCT02624401.

Keywords: cerebral blood flow; cerebral metabolism; positron emission tomography; sedation; target-controlled infusion

Editor's key points

- The effects of dexmedetomidine, propofol, S-ketamine, and sevoflurane on the regional cerebral metabolic rate of glucose (CMR_{glu}) were compared at equi-sedative doses.
- All but S-ketamine reduced cerebral metabolic rate relative to placebo with relative potencies of dexmedetomidine>propofol>ketamine=placebo.
- Sevoflurane decreased metabolism equally to propofol but the dose was not quite equipotent.
- These findings alleviate concerns for harmful effects of dexmedetomidine on the ratio of cerebral blood flow and metabolism.

Different anaesthetics produce characteristic effects on cerebral blood flow (CBF) and metabolism. While sevoflurane decreases cerebral metabolism more than CBF,[1–4] propofol induces a proportional decrease in both measures.[1–3,5–11] For this reason, propofol has been deemed particularly suitable for neurosurgical and neurointensive care patients. S-ketamine has been demonstrated to increase glucose metabolism in certain regions of the brain and to induce a global increase in CBF.[12–14] Although dexmedetomidine has become a popular sedative for neurointensive care patients, its effects on cerebral glucose metabolism have not been properly characterised in humans.

Dexmedetomidine is an α_2-adrenoceptor agonist with unique properties; it induces sufficient sedation while allowing patient arousal and awakening without changing infusion rate. This is a valuable feature, especially in intensive care patients, who need frequent assessment of their neurological state. In addition, dexmedetomidine has mild analgesic properties and minimal respiratory effects. Furthermore, experimental studies have suggested neuroprotective properties of dexmedetomidine,[15] but this has not been established in humans.[16] In early animal studies, dexmedetomidine was found to reduce CBF with no effect on the cerebral metabolic rate of oxygen.[17,18] This raised concern that the decreased blood flow might be inadequate for the cerebral metabolic needs. Studies in humans have, however, suggested that dexmedetomidine proportionally decreases CBF and oxygen metabolism.[19,20] Nevertheless, uncertainty remains on this issue.

We compared the effects of dexmedetomidine, propofol, sevoflurane, S-ketamine, and placebo on the regional cerebral metabolic rate of glucose (CMR_{glu}) with high-resolution positron emission tomography (PET) imaging. Our aim was to establish the relative potencies of these four anaesthetics with different mechanisms of action, all given at equi-sedative doses.

Methods

Trial design and participants

We conducted an open-label, randomised, controlled, parallel group, phase IV clinical drug trial at the Turku PET Centre, University of Turku, Finland. The study (ClinicalTrials.gov Identifier NCT02624401) was approved by the Ethics Committee of the Hospital District of Southwest Finland and the Finnish Medicines Agency Fimea (EudraCT 2015-004982-10).

Inclusion criteria were male sex, age 18–30 yr, normal hearing, right handedness, good sleep quality, ASA physical status class 1, fluency in the Finnish language and normal results in a thorough physical examination and laboratory tests including drug screening. Use of any medication or alcohol was prohibited for 48 h and caffeine products for 10–12 h before the study session. All subjects fasted from the previous midnight. Written informed consent was obtained from all subjects according to the Declaration of Helsinki.

The goal was to have 160 ($n=40$ in each group, except $n=20$ in the S-ketamine and placebo groups) subjects with complete data, and because of 20 premature withdrawals or dropouts (see Results), 180 subjects were recruited. Subjects were randomised with balanced permuted block sizes of 16 to receive either dexmedetomidine (Dexdor 100 μg ml^{-1}; Orion Pharma, Espoo, Finland), propofol (Propolipid 10 mg ml^{-1}; Fresenius Kabi, Uppsala, Sweden), sevoflurane (Sevorane 100%; Abbvie, Espoo, Finland), S-ketamine (Ketanest-S 25 mg ml^{-1}; Pfizer, Helsinki, Finland) or saline placebo. The person (H.S.) responsible for randomisation did not recruit the subjects to ensure random allocation of the treatments. Baseline characteristics of the subjects are shown in Table 1.

Anaesthetic protocol and monitoring

A radial artery was cannulated for all blood samplings and two forearm venous catheters were placed for administration of anaesthetics and Ringer's acetate (at a standard rate of ~100 ml h^{-1}), and ^{18}F-labelled fluorodeoxyglucose ([^{18}F]FDG). Subjects breathed room air.

Table 1 Height, weight and age of subjects

	Number of subjects	Height (cm)		Weight (kg)		Age (yr)
		Mean	SD	Mean	SD	Range
Dexmedetomidine	40	179.1	6.5	77.3	10.8	20–30
Propofol	40	180.5	6.0	77.6	11.1	18–28
Sevoflurane	40	179.7	7.2	79.5	9.7	19–30
S-Ketamine	20	182.7	5.4	79.9	10.6	20–30
Placebo	20	182.4	8.8	82.9	14.2	20–28

The study outline and sequence of events are shown in Fig. 1. The drug administration protocol included a 20 min stabilisation phase, followed by a 40 min pseudosteady-state phase. I.V. anaesthetics were administered using target-controlled infusion with a Harvard 22 syringe pump (Harvard Apparatus, South Natick, MA, USA) connected to a portable computer running Stanpump software (www.opentci.org/code/stanpump) with previously reported pharmacokinetic parameters.[21–23] In each of the drug groups, the aim was to achieve a sample where 50% of subjects were unresponsive and 50% maintained responsiveness, defined as the 50% effective concentration for loss of responsiveness (LOR) to verbal command (i.e. $EC_{50\ for\ LOR}$) or minimum alveolar concentration (MAC) for LOR (i.e. MAC_{LOR}) for sevoflurane. The selected $EC_{50\ for\ LOR}$ values were based on previous studies: 1.5 ng ml^{-1} for dexmedetomidine, 1.7 μg ml^{-1} for propofol, and 0.75 μg ml^{-1} for S-ketamine.[12,24,25] Sevoflurane was administered at an end-tidal MAC_{LOR} target of 0.9%.[24] Sevoflurane group subjects wore a face mask tightened with a rubber strap with fresh gas flow set at 6 L min^{-1}. After 60 min of drug administration, subjects were transferred to the PET scanner room for a 30 min PET scan (see below).

Peripheral oxygen saturation, ECG, and end-tidal carbon dioxide were monitored continuously during the study. Blood pressure was measured non-invasively at the beginning and end of drug administration to avoid possible cuff pain and ensuing arousal during PET data acquisition. A Datex-Ohmeda S/5 anaesthesia monitor (Datex-Ohmeda Division, Instrumentarium Corp., General Electric Company, Helsinki, Finland) and a portable computer running the S5 Collect software (Collect version 4.0, GE Healthcare) were used to record and store all vital parameters.

Subjects were classified as responsive or unresponsive by asking them to press a custom-made handle secured on both wrists. A prerecorded request 'press the handles twice' was delivered via headphones using the Presentation 17.0 stimulus delivery and experimental control software system (Neurobehavioral Systems Inc, Berkeley, CA, USA). Testing was

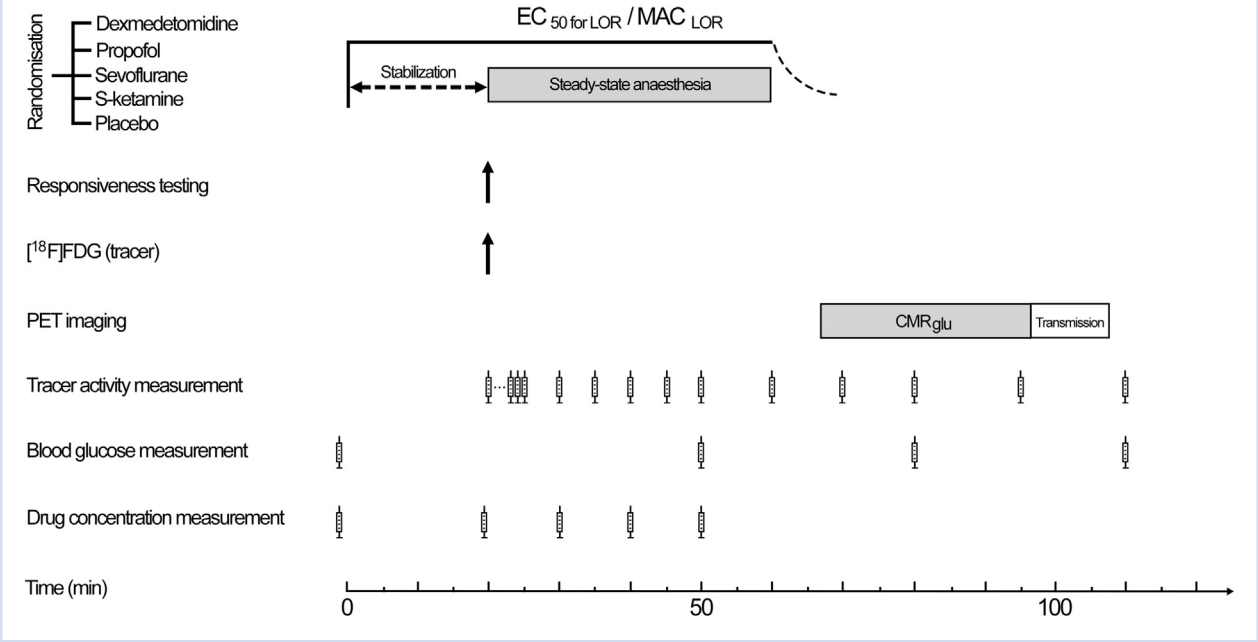

Fig 1. Study design, sequence of events and timing of measurements and blood samples. $EC_{50\ for\ LOR}$, Effective concentration 50 for loss of responsiveness; MAC_{LOR}, minimum alveolar concentration for LOR; [^{18}F]FDG, ^{18}F-labeled fluorodeoxyglucose; CMR_{glu}, cerebral metabolic rate of glucose; PET, positron emission tomography.

performed just before injection of [^{18}F]FDG. Concentrations of the i.v. anaesthetics in plasma were determined at baseline and at 19, 30, 40 and 50 min after start of the infusion using validated methods. High-performance liquid chromatography (HPLC) with tandem mass spectrometry was used for dexmedetomidine and S-ketamine. Propofol concentrations were measured with HPLC and fluorescence detection. Interassay coefficients of variation in the relevant concentration ranges were 1.2–2.9%, 3.7–8.0% and 0.7–2.2%, respectively.

PET data acquisition and assessment

[^{18}F]FDG was used as the PET tracer to quantify CMR_{glu} in 15 brain regions of interest (ROIs). ^{18}F was produced by irradiating enriched [^{18}O]H_2O with protons (cyclotron CC 18/9, D.V. Efremov Institute, St. Petersburg, Russia). [^{18}F]FDG was synthesised according to GMP regulations using an automated synthesis device (Fastlab; GE Healthcare, Chicago, IL, USA). Radiochemical purity of the product exceeded 95%. Anatomical reference MRI were obtained from each participant separately with a Philips Ingenuity PET-MR 3T scanner (Philips Medical Systems, Best, The Netherlands).

The 300 MBq dose of [^{18}F]FDG was administered 20 min after commencement of drug administration using a Rad Injector (Tema Sinergie, Faenza, Italy). A Karl100 (Tema Sinergie, Faenza, Italy) device was used for safe dispensing of the radiopharmaceutical into a shielded syringe. After the 40 min pseudo-steady-state phase, retention of [^{18}F]FDG was considered to be stabilised, administration of anaesthetic was terminated, and a 30 min PET scan was performed followed by a transmission scan using a High Resolution Research Tomograph, a dual-layer crystal-detector scanner with an isotropic 2.5 mm intrinsic spatial resolution (HRRT; Siemens Medical Solutions, Knoxville, TN, USA).[26,27] The time lag between the end of anaesthesia and the start of PET scanning was 5–10 min.

All study sessions were conducted in a quiet, dimly lit room. PET emission data acquisition in list-mode format was initiated approximately 45–50 min after tracer injection. The subject's head was fixed to the headrest of the scanner with an individual thermoplastic mask made before the scanning. Head motion was monitored using a high-precision, stereotactic tracking device (Polaris Vicra; Northern Digital, Waterloo, Ontario, Canada) attached to the subject's head. Image formation was conducted using an iterative OP-OSEM algorithm with resolution modelling (12 iterations, 16 subsets, including corrections for attenuation, scatter, and random events).[28] PET emission data were histogrammed into a single 30 min frame reflecting the assumption of steady [^{18}F]FDG retention at this late time window. If a head movement >2.5 mm was detected, scans were divided into subframes and subsequently co-registered into a single 30 min frame by using the multiple acquisition frame image reconstruction procedure and the attenuation correction realignment algorithm.[29] This procedure was used in four dexmedetomidine scans, two S-ketamine scans, and two sevoflurane scans.

Twenty-four arterial tracer activity blood samples were collected for tracer kinetic modelling. Immediately after the injection of [^{18}F]FDG, the first 12 samples were obtained at intervals of 15 s, followed by additional samples at 4, 5, 10, 15, 20, 25, 30, 35, 40, 50, 60, 75, and 90 min. In addition, samples were drawn to measure plasma glucose concentrations at baseline, and at 30, 60, and 90 min after the injection of [^{18}F]FDG.

Data analysis

Calculation of voxel-wise maps of CMR_{glu} was conducted on the basis of average [^{18}F]FDG retention at 50–80 min after tracer injection and plasma radioactivity data. Individual MRIs were then co-registered with the parametric images of subjects using statistical parametric mapping software (version 8, SPM8; Wellcome Institute, London, UK).

The voxel-wise maps of CMR_{glu} were calculated according to the equation[30]

$$CMR_{glu} = \frac{FUR \times C_{glu}}{LC} \quad (1)$$

where FUR is the fractional uptake rate of [^{18}F]FDG relative to the integral (0–90 min) of [^{18}F]FDG concentration in plasma, C_{glu} is plasma glucose concentration, and LC is the lumped constant (0.65).[31] Using the average brain tissue density (1.04 g ml^{-1}), CMR_{glu} values were converted into units of μmol 100 g^{-1} min^{-1}.

Voxel-average, regional CMR_{glu} values were extracted within 15 ROIs including the prefrontal cortex, parietal cortex, lateral temporal cortex, lateral occipital cortex, precuneus, anterior cingulate gyrus, posterior cingulate gyrus, entorhinal cortex, striatum, cerebellum, insula, thalamus, amygdala, pallidum, and hippocampus. ROIs were generated automatically with the help of individual T1-weighted MRI data and FreeSurfer software (version 5.3; http://surfer.nmr.mgh.harvard.edu/; see Supplementary material).

Statistical analyses

The statistical analyses of regional CMR_{glu} data were performed with analysis of variance (ANOVA). First, all regions were analysed together using repeated measures ANOVA with region as a within factor and treatment as a between factor. If a

Table 2 Targeted and measured concentrations of dexmedetomidine, propofol, S-ketamine, and sevoflurane at baseline and at four time points (19, 30, 40, and 50 min) after commencing drug administration

	Number of subjects	Baseline		19 min		30 min		40 min		50 min		Targeted
		Mean	SD	Mean	SD	Mean	SD	Mean	SD	Mean	SD	
Dexmedetomidine (ng ml^{-1})	40	0.00	0.00	2.17	0.43	2.13	0.37	2.09	0.35	2.06	0.34	1.50
Propofol (μg ml^{-1})	40	0.00	0.00	1.82	0.38	1.74	0.35	1.73	0.36	1.73	0.37	1.70
Sevoflurane (end-tidal%)	40	0.00	0.00	0.90	0.05	0.92	0.05	0.90	0.04	0.91	0.04	0.90
S-Ketamine (μg ml^{-1})	20	0.00	0.00	0.85	0.18	0.99	0.18	1.04	0.21	1.04	0.22	0.75

Table 3 Cerebral metabolic rate of glucose (μmol 100 g^{-1} min^{-1}) in the dexmedetomidine, propofol, sevoflurane, S-ketamine, and placebo groups. Tukey-corrected *P*-values for significant paired comparisons (*drug *vs* placebo) and between drugs (†dexmedetomidine *vs* propofol, ‡dexmedetomidine *vs* sevoflurane, ¶drug *vs* S-ketamine). The number of symbols refer to level of significance (e.g. *P<0.05, **P<0.01 and ***P<0.001). °Degrees of freedom

Brain area	Dexmedetomidine				Propofol				Sevoflurane				S-Ketamine				Placebo		One-way ANOVA	
	Mean	SD	% of placebo		Mean	SD	% of placebo		Mean	SD	% of placebo		Mean	SD	% of placebo		Mean	SD	F (4,155)°	P-value
Prefrontal cortex	23.7	2.0	62.4	***, †††, ‡‡‡, ¶¶¶	27.1	3.5	71.2	***, ¶¶¶	27.2	4.3	71.5	***, ¶¶¶	36.3	7.1	95.5		38.0	3.9	72.47	<0.001
Parietal cortex	23.2	2.1	61.6	***, ††, ‡‡, ¶¶¶	25.9	3.8	68.7	***, ¶¶¶	26.2	4.4	69.6	***, ¶¶¶	37.9	8.0	100.4		37.7	3.4	88.49	<0.001
Lateral temporal cortex	21.4	2.0	64.9	***, †††, ‡‡, ¶¶¶	24.1	3.6	72.8	***, ¶¶¶	23.8	3.8	72.0	***, ¶¶¶	31.8	5.8	96.3		33.1	3.0	70.76	<0.001
Lateral occipital cortex	21.6	1.9	62.9	***, ¶¶¶	22.7	3.3	66.2	***, ¶¶¶	23.0	3.9	67.0	***, ¶¶¶	34.2	6.7	99.5		34.3	3.4	72.94	<0.001
Precuneus	24.8	2.3	60.6	***, †††, ‡‡‡, ¶¶¶	27.9	3.8	68.2	***, ¶¶¶	28.3	4.6	69.0	***, ¶¶¶	40.3	8.2	98.3		41.0	4.1	80.49	<0.001
Anterior cingulate gyrus	19.9	1.7	65.2	***, †††, ‡‡‡, ¶¶¶	24.0	3.3	78.6	***, ¶¶	23.4	3.5	76.6	***, ¶¶¶	29.1	5.5	95.3		30.5	3.1	67.21	<0.001
Posterior cingulate gyrus	23.3	2.4	60.7	***, †††, ‡‡‡, ¶¶¶	26.7	3.6	69.6	***, ¶¶¶	26.7	4.0	69.5	***, ¶¶¶	36.3	6.6	94.5		38.4	4.1	70.15	<0.001
Entorhinal cortex	14.6	1.6	66.3	***, †††, ‡‡‡, ¶¶¶	17.1	2.5	77.9	***, ¶¶¶	16.6	2.8	75.8	***, ¶¶¶	20.6	3.0	93.9		22.0	2.9	41.73	<0.001
Striatum	22.5	2.2	64.1	***, †††, ‡‡‡, ¶¶¶	27.7	3.7	78.8	***, ¶¶	26.8	4.4	76.4	***, ¶¶	32.6	6.1	93.0		35.1	4.1	57.13	<0.001
Cerebellum	16.3	1.6	62.6	***, †††, ¶¶¶	18.8	2.6	72.3	***, ¶¶¶	17.6	2.7	67.7	***, ¶¶¶	23.7	3.0	90.9		26.1	2.9	68.84	<0.001
Insula	20.4	1.9	65.7	***, †††, ‡‡, ¶¶¶	23.5	3.0	75.6	***, ¶¶¶	22.8	3.6	73.5	***, ¶¶¶	28.9	5.2	93.2		31.0	3.0	61.56	<0.001
Thalamus	17.8	1.6	60.4	***, †††, ‡‡, ¶¶¶	21.2	3.1	71.9	***, ¶¶¶	19.9	3.6	67.4	***, ¶¶¶	29.6	5.0	100.3		29.5	3.5	76.28	<0.001
Amygdala	14.1	1.3	69.9	***, †††, ‡‡, ¶¶¶	16.4	2.2	81.3	***	15.6	2.5	77.5	***, ¶¶	18.4	3.2	91.3		20.2	2.2	39.51	<0.001
Pallidum	15.6	2.3	64.7	***, †††, ‡, ¶¶¶	18.6	2.8	77.2	***, ¶¶¶	17.5	3.1	72.8	***, ¶¶¶	23.4	4.4	97.4		24.1	3.3	36.32	<0.001
Hippocampus	15.5	1.3	67.7	***, †††, ‡‡, ¶¶¶	17.6	2.3	77.0	***, ¶	17.1	2.5	74.9	***, ¶¶	20.4	3.5	89.2		22.9	2.4	48.46	<0.001
Whole brain	21.2	1.8	62.8	***, †††, ‡‡, ¶¶¶	24.1	3.2	71.4	***, ¶¶¶	23.8	3.7	70.5	***, ¶¶¶	32.3	5.6	95.9		33.7	3.1	81.42	<0.001

significant region by treatment interaction was found, the analyses were continued for each region separately and for the whole brain CMR_{glu} (aggregate of all 15 ROIs) using one-way ANOVA with treatment as a between factor followed by paired comparisons of the different treatments using Tukey's *post hoc* tests for multiple correction. For i.v. anaesthetics, Pearson correlation coefficients were calculated to assess the association between the mean measured drug concentration and whole brain CMR_{glu}, and χ^2 testing was used to compare responsiveness at the time of [^{18}F]FDG injection between treatments. The normality of variables was checked using the Kolmogorov–Smirnov test. A two-sided $P<0.05$ was considered statistically significant. Results are given as mean (standard deviation [SD]) if not stated otherwise. Statistical analyses were performed with SAS System for Windows, version 9.4. (SAS Institute Inc., Cary, NC, USA).

Results

Of 180 subjects recruited, 15 withdrew from the study after randomisation. Four sessions (three with S-ketamine, one with sevoflurane) had to be terminated because of excessive motor anxiety. In addition, one subject received only approximately 7% of the planned S-ketamine dose because of a programming error and was therefore excluded. Otherwise, the study was completed as planned. No clinically significant changes were observed in vital parameters (data not shown).

One hundred and sixty subjects were evaluable (40 dexmedetomidine, 40 propofol, 40 sevoflurane, 20 S-ketamine, and 20 placebo) for regional CMR_{glu}. Measured dexmedetomidine and S-ketamine concentrations were somewhat higher than targeted (Table 2). At the time of [^{18}F]FDG injection, 22 (55%) dexmedetomidine, 18 (45%) propofol, 34 (85%) sevoflurane, nine (45%) S-ketamine, and 0 (0%) placebo subjects were unresponsive to verbal command [$\chi^2(4)=40.43$, $P<0.001$]. In paired comparisons, all drugs differed from placebo and sevoflurane differed from the other drugs.

Because a significant region by treatment interaction ($P<0.001$) was found in the repeated measures ANOVA, regions were analysed separately. There were statistically significant differences in regional CMR_{glu} between groups in all 15 ROIs and their aggregate (whole brain CMR_{glu}; $P<0.001$ for all; Table 3, Figs. 2 and 3). In paired comparisons, the dexmedetomidine, propofol and sevoflurane groups differed from the placebo and S-ketamine groups. Dexmedetomidine was associated with the lowest CMR_{glu} in all brain regions and differed from all other drugs ($P<0.05$), with the exception that no significant difference was found in the lateral occipital cortex compared with propofol or sevoflurane, and in the cerebellum compared with sevoflurane (Table 3). Compared with placebo, regional CMR_{glu} values were 30.1–39.6% lower in the dexmedetomidine group. Propofol and sevoflurane did not differ from each other in any ROI. With S-ketamine, CMR_{glu} did not differ from placebo in any of the ROIs studied. There were weak but statistically significant associations between measured drug concentrations and CMR_{glu} in the dexmedetomidine and propofol groups (Fig. 4).

Discussion

The effects of EC_{50} doses for LOR of dexmedetomidine, propofol, sevoflurane, and S-ketamine on absolute CMR_{glu} were evaluated using state-of-the-art PET methodology. Compared with placebo, significantly lower CMR_{glu} values were measured with dexmedetomidine, propofol, and sevoflurane throughout the brain. The greatest suppressive effect was seen with dexmedetomidine, which induced the lowest CMR_{glu} in

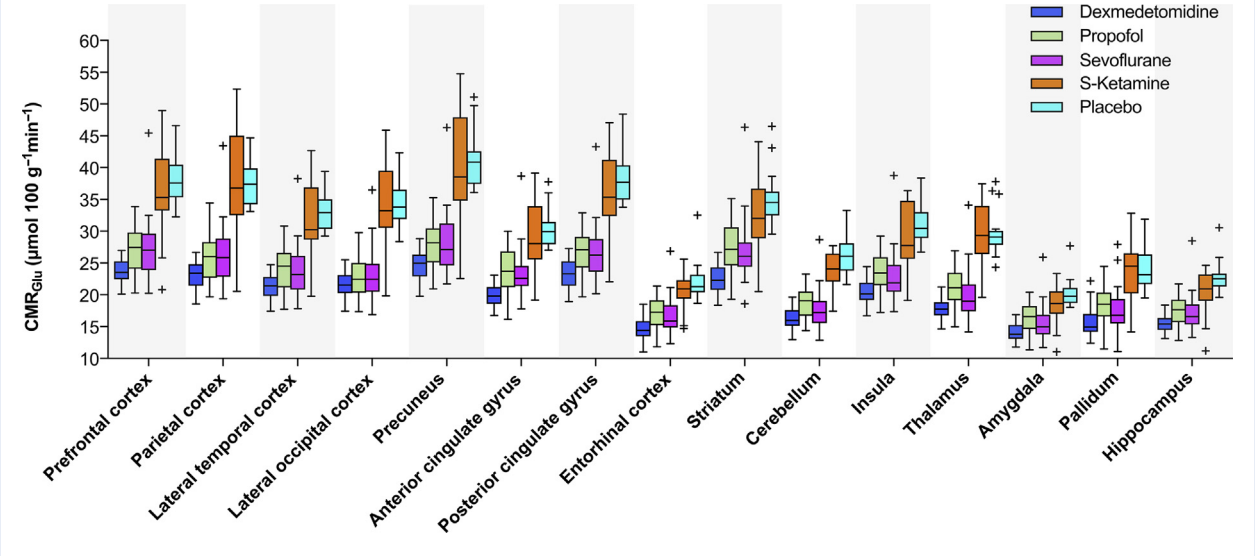

Fig 2. Boxplots of regional cerebral metabolic rate of glucose (CMR_{glu}) in the 15 analysed regions of interest (ROIs) during dexmedetomidine, propofol, sevoflurane, S-ketamine, and placebo administration in 160 healthy subjects ($P<0.001$ between the treatments in all ROIs). Lowest CMR_{glu} values were observed in the dexmedetomidine group (for paired comparisons, see Table 3). Boxes represent lower quartiles, medians and upper quartiles, whiskers represent 1.5×inter-quartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with symbols.

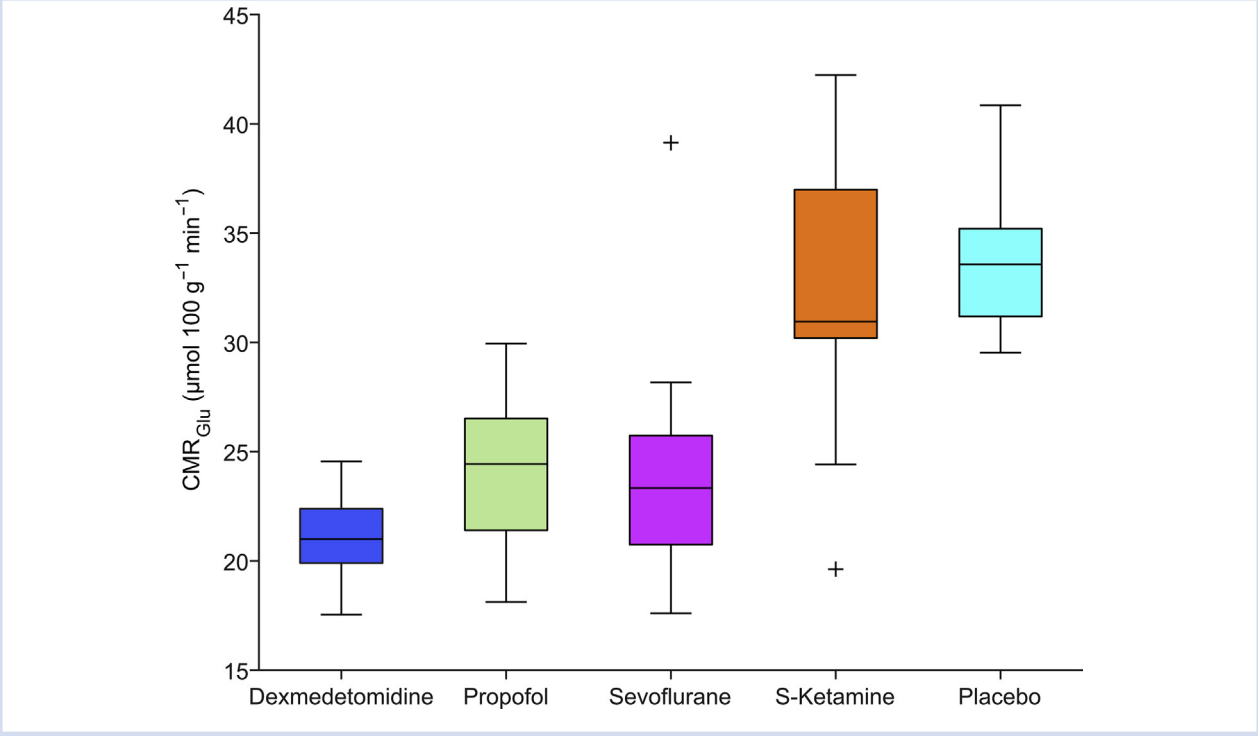

Fig 3. Boxplots of whole brain cerebral metabolic rate of glucose (CMR_{glu}) in 160 healthy subjects. CMR_{glu} was 63%, 71%, 71%, and 96% of placebo, in the dexmedetomidine, propofol, sevoflurane, and S-ketamine groups, respectively ($P<0.001$ between the groups). Dexmedetomidine differed from all other groups (for paired comparisons, see Table 3). Boxes represent lower quartiles, medians and upper quartiles, whiskers represent 1.5×inter-quartile ranges below and above the lower and upper quartiles, respectively. Outlying values are marked with symbols.

nearly all brain regions compared with the other groups. With S-ketamine, CMR_{glu} values were comparable with placebo.

Previous studies in laboratory animals and humans have quite consistently demonstrated that dexmedetomidine decreases CBF.[17–19,32,33] The most convincing evidence was seen in an early human PET study where a 0.628 ng ml^{-1} average plasma concentration of dexmedetomidine resulted in a 33% global decrease in CBF from baseline.[32] A reduction in CBF has also been demonstrated with the sagittal sinus outflow technique in two early studies in dogs where dexmedetomidine was given during isoflurane[18] or halothane[17] anaesthesia. The most remarkable finding in these studies was that the decrease in CBF was not associated with a concomitant decrease in cerebral oxygen metabolism, which raised concern that dexmedetomidine might cause ischaemia in the brain.[17,18] In healthy brain with functional flow-metabolism coupling, a reduction in neuronal activity should be accompanied by a parallel decrease in cerebral metabolism and, consequently, CBF.[34] Dexmedetomidine is known to cause direct vasoconstriction of the cerebral vessels through

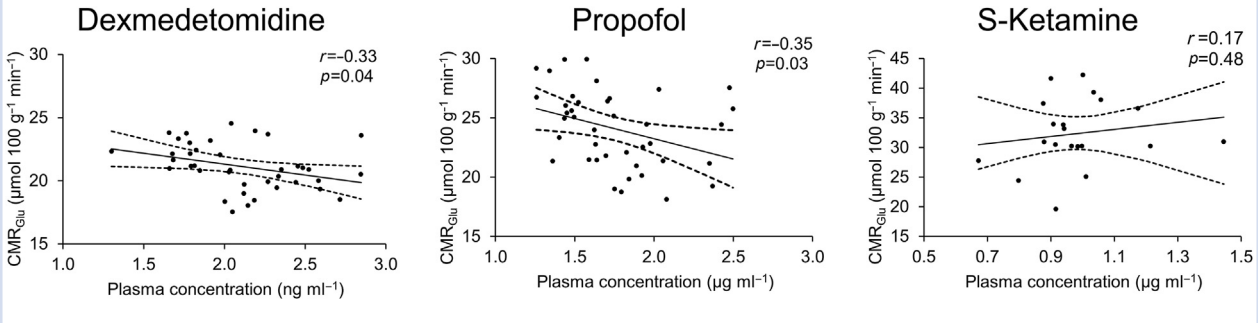

Fig 4. Correlation plots of the associations between the mean measured drug concentration of dexmedetomidine, propofol, and S-ketamine and whole brain cerebral metabolic rate of glucose (CMR_{glu}). r=Pearson correlation coefficient; dashed lines depict the 95% confidence intervals for the regression lines.

activation of postsynaptic α_2-adrenoreceptors on vascular smooth muscle cells,[35] which, in the absence of a concomitant reduction in cerebral metabolism, might predispose the brain to ischaemia. For this reason, a better understanding regarding the effects of dexmedetomidine on brain metabolism is needed. This would have implications for treatment of patients with compromised brain function who are at high risk for cerebral ischaemia.

Two small clinical trials have addressed the relationship between brain oxygen utilisation and CBF during dexmedetomidine exposure. By using the middle cerebral artery flow velocity technique and oxygen metabolism equivalent estimation based on jugular vein blood samples, it was demonstrated in six healthy human subjects that dexmedetomidine might decrease cerebral oxygen metabolism equivalently to CBF.[19] Another study showed that dexmedetomidine did not affect brain tissue oxygen concentration in five neurosurgical patients.[36] While these studies were limited by their small sample size, the first study could only offer global relative values and the second study contained many confounding elements including concomitant surgery. Although the latter study could not measure metabolism *per se*, the preliminary results suggested that dexmedetomidine would not have a direct vasoconstrictive effect that might lead to diminished oxygen delivery to brain tissue.

The most sophisticated previous study on the subject was conducted using combined imaging of CBF with the arterial spin labelling functional MRI technique and [^{18}F]FDG-PET.[37] Dexmedetomidine-induced suppression of CBF and CMR_{glu} was observed in the thalamus, the default mode network structures and the frontoparietal regions bilaterally. However, because PET imaging was performed without blood activity sampling, this study could not determine the absolute regional CMR_{glu} effects of dexmedetomidine. The present study resolves this shortcoming and was able to show a significant reduction in absolute regional CMR_{glu}. Given that parallel reductions in CBF have been reported previously,[17–19,32,37] the present results alleviate concern for potential harmful effects of dexmedetomidine on coupling between brain metabolism and perfusion.

Numerous studies have shown that propofol and volatile anaesthetics decrease CMR_{glu}, cerebral oxygen metabolism, and CBF.[1–11,38,39] Our results are in line with these previous findings. Ketamine or S-ketamine increase CBF, while their metabolic effects are limited to only a slight increase in certain brain regions.[12–14] Thus, the present results with S-ketamine, with effects on CMR_{glu} comparable with placebo, are also in agreement with previous findings. However, it is noteworthy that the greatest individual variability in CMR_{glu} was observed in the S-ketamine group (Fig. 2). Here, we provide a definitive answer to anaesthetic potency for reducing CMR_{glu}. Potency for CMRglu reduction in humans follows the rank order of dexmedetomidine>propofol>ketamine=placebo. Sevoflurane decreased metabolism equally to propofol, but the dose was not quite equipotent.

The main limitation of this study was that CBF was not measured together with CMR_{glu}. Thus, we still lack knowledge of the exact metabolism–perfusion effects of dexmedetomidine. However, the clear reduction in CMR_{glu} observed shows that a parsimonious mode of brain activity can be achieved with dexmedetomidine. Second, only healthy male subjects were investigated. The most concerning issue is the direct vasoconstrictive effect of dexmedetomidine, which might increase the risk of cerebral ischaemia, for example in patients with aneurysmal subarachnoid haemorrhage already vulnerable to vasospasm. Still, reduction in brain activity and CMR_{glu} would probably offer some protection against such an effect. Third, measurements were made for only one target concentration of each of the four anaesthetics. Fourth, our goal of comparing equipotent doses ($EC_{50\ for\ LOR}$ or MAC_{LOR}) of anaesthetics was not quite met as 85% of the sevoflurane subjects were unresponsive at the time of [^{18}F]FDG injection, compared with 45–55% in the other drug groups. Despite this shortcoming, CMR_{glu} in the dexmedetomidine group was significantly lower than in the sevoflurane group in the whole brain and in 13 of the 15 ROIs studied.

In conclusion, dexmedetomidine, propofol, and sevoflurane decreased CMR_{glu} in a global manner compared with placebo and S-ketamine, with dexmedetomidine inducing the greatest suppression. The present results alleviate the concern for potential harmful effects of dexmedetomidine on the ratio of cerebral blood flow and metabolism.

Authors' contributions

Subject recruitment, data collection, and writing the manuscript: L.L.
Data analysis and writing the manuscript: M.K., M.A.
Data collection and writing the manuscript: J.L., T.L., A.S., J.S.
Data collection and review of the manuscript: A.M., K.K., O.K., R.K., V.R., K.V.
Laboratory analysis and review of the manuscript: S.S.
Data analysis and review of the manuscript: J.J., M.N., T.V.
Study design and review of the manuscript: A.R., O.S.
Principal investigator, study design, data analysis, writing the manuscript: H.S.
Review and approval of the final draft of manuscript: all authors.

Acknowledgements

The authors thank the radiographers and anaesthesia nurses at Turku University Hospital for excellent technical assistance.

Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.bja.2018.04.008.

Declaration of interest

Dr. Jaakko Långsjö has received a lecture compensation from Orion Pharma and attented an educational congress as a quest of Pfizer. Dr. Långsjö also reports to be a minor shareholder of Orion. Dr. Timo Laitio is a paid consultant of NeuroproteXeon. The rest of the authors declare that they have no conflicts of interest.

Funding

This work was supported by Academy of Finland, Helsinki, Finland (grant numbers 266467, 266434); Jane and Aatos Erkko Foundation, Helsinki, Finland; VSSHP-EVO (grant numbers 13323, L3824), Turku, Finland; Doctoral Programme of Clinical Investigation, University of Turku Graduate School, Turku, Finland (A.S.); The Finnish Medical Foundation, Helsinki, Finland (J.L.); The Emil Aaltonen Foundation, Tampere, Finland (J.L.); and The Paulo Foundation, Espoo, Finland (A.M.).

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Handling editor: H.C. Hemmings Jr