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REVIEW

Cerebral microdialysis values in healthy brain tissue – a scoping review

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Abstract

Background Intracerebral microdialysis is an advanced method to guide clinicians during intensive care of patients with severe acute brain injury. Using intracerebral microdialysis, markers of brain metabolism and homeostasis can be analysed. Currently, trends are considered more important in clinical decision-making than absolute values. Establishing absolute reference values in healthy brain tissue may facilitate an earlier detection of abnormal brain tissue metabolism and provide better decision support for clinicians. However, the current evidence on normal values in the uninjured human brain has not previously been summarized. The aim of this study was to summarise the literature regarding microdialysate concentrations of common markers of brain energy metabolism (glucose, lactate, pyruvate, glutamate, and glycerol) in vivo in healthy brain tissue of humans and gyrencephalic animals.

Method MEDLINE, Embase, CENTRAL, CINAHL, and Web of Science were searched for published studies that report values of microdialysis in healthy brain tissue. In order to identify unpublished studies, we searched ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), and EU Clinical Trials Register. Study quality was evaluated using a pre-specified protocol.

Result Out of 3257 studies identified, 39 studies were included. Six of these studies were in humans (total $n = 54$), 26 in pigs/swine ($n = 432$), two on monkeys ($n = 10$), one in sheep ($n = 15$), and one in dogs ($n = 10$). We found a high degree of clinical and methodological heterogeneity in both human and gyrencephalic animal studies.

Conclusion This scoping review identified studies that applied microdialysis to measure common biomarkers in healthy brain tissue. The clinical and methodological heterogeneity between the measured values was substantial, limiting any conclusions. Furthermore, the quality of several human studies was moderate at best. Methodologically comparable studies are warranted to establish reference values for markers of brain energy metabolism using intracerebral microdialysate.

Keywords Cerebral microdialysis · Biomarkers · Healthy brain tissue · Gyrencephalic animals · Humans

Abbreviations

ABI Acute brain injury
LPR Lactate-pyruvate ratio
ZFM Zero flow method

Background

Severe acute brain injury (ABI) encompasses conditions that cause sudden, severe damage to the brain, such as physical trauma, spontaneous intracranial haemorrhage, and hypoxic or ischaemic injury. The patient population is relatively young, likely to be hospitalized in an intensive care unit [30, 33], and at high risk of dying or surviving with severe functional deficit [38, 41]. Although severe ABI is a relatively rare condition, the burden and social economic losses are enormous for the individual, the family, and the society [19, 23]. The treatment of this patient population is expensive and complicated, and improving the care for this patient population should therefore be a priority.

Both primary and secondary brain injuries are important determinants of outcome. Secondary brain injury comprises

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activation of processes that occur after the initial event, and which are generally assumed to be preventable to some degree [33]. Monitoring brain energy metabolism and homeostasis may increase the chance both of detecting secondary brain injury at an early stage, before it manifests clinically, and of preventing and monitoring its progress. To this end, intracerebral microdialysis is today the only bedside tool that can monitor brain energy metabolism and homeostasis. This is done by a catheter that is placed in the brain tissue and perfused with microdialysate typically at a flow at 0.3 μL min^{-1} to 5 μL min^{-1}. The catheter has a double lumen, whose outer layer contains a semipermeable membrane with pores of a well-defined size (typically 20 or 100 kDa) [17]. This membrane acts like a capillary and allows partial equilibration of molecules between the extracellular fluid in the brain tissue and the microdialysate. The perfusion rate and the pore size of the membrane are both crucial for the relative recovery, i.e., the efficiency with which the biomarkers are extracted to the microdialysate from the extracellular fluid [40]. The microdialysate is subsequently collected in microvials and analysed for different biomarkers, enabling adjustment of treatment.

Currently, trends in common biomarkers such as glucose, lactate, pyruvate, lactate-pyruvate ratio, glutamate, and glycerol are considered more important than absolute values for such clinical decision-making [4, 56]. However, establishing normal absolute values for these biomarkers may potentially further improve the value of this tool in the clinical setting.

The aim of this scoping review was to systematically assess the literature reporting normal values of glucose, lactate, pyruvate, LPR, glutamate, and glycerol in intracerebral microdialysis in healthy brain tissue.

Method

The protocol was registered at the Open Science Framework (OSF), https://doi.org/https://doi.org/10.17605/OSF.IO/M9PRT. We followed guidelines from Peters et al. [42] and The Joanna Briggs Institute Manuale [43] and divided our scoping review into five stages: 1) Identifying the research question, 2) Identifying relevant studies, 3) Study selection, 4) Charting data, and 5) Analysing and presenting data.

Eligibility criteria

The eligibility criteria were defined using people/concept/context framework (PCC) recommended by JBI review manual [43], see Table 1. We expected to find sparse human data; therefore, our population included both humans and gyrencephalic animals.

For humans, because ethical considerations preclude intracerebral microdialysis in healthy volunteers, we chose to expand the search to include studies in patients with focal brain injury. "Focal brain injury" was defined as localised changes in brain tissue in one hemisphere, which could be assumed not to affect oxidative metabolism in the contralateral hemisphere. Presumably unaffected brain tissue from such patients was referred to as healthy brain tissue, and the study was included if at least one microdialysis catheter was placed in this tissue.

Search strategy

We searched the following five databases: MEDLINE; Embase, CENTRAL, CINAHL and Web of Science, using a search string developed with help of a librarian from the Danish Medicine Library, and modified to each database and further searched the reference lists of the included studies. We also searched for unpublished studies at ClinicalTrials.gov, WHO International Clinical Trials Registry Platform (ICTRP), and EU Clinical Trials Registry, and the reference lists of included trials. The search string is presented in Online Resource 1.

Screening method

All identified studies were uploaded to Covidence [8] and duplicates removed. Three independent authors (ILG, HRJ, MLF – two per study) screened for title, abstract and full text, and any discrepancy was solved by consulting a third senior author (MKS).

Table 1 Eligibility criteria

People/participants	Healthy humans Humans with a focal brain injury Gyrencephalic animals
Concept	Microdialysis measurements of glucose, lactate, pyruvate, LPR, glutamate, and glycerol in presumably healthy brain tissue
Context	All studies, that in relation to clinical trials or as routine clinical care, investigating values defined above. Also, animal trials that have taken baseline values before any intervention will be included. Only steady-state measurements are included

Data charting, critical appraisal, and reporting of data

Data from the included studies were charted using a pretested data charting form. For human studies, we collected demographic data such as age, sex and diagnosis. For gyrencephalic animals, we collected data on the animal species, race, age, sex and weight. For both human studies and animal studies, we collected data on anaesthesia, microdialysis catheter type and anatomical location, equilibration time, membrane permeability, perfusion rate, type and timing of biomarker analysis, and measured concentrations of biomarkers (for details see Online Resource 2). For the latter, only values that could be assumed to be measured at steady state were recorded. Any discrepancy was solved with the senior author (MKS). Measurements presented in figures, and where the authors did not reply to our attempts to obtain quantitative data, were extracted by using PlotDigitizer [44], as recommended by Cochrane [29]. Furthermore, we critically appraised the quality of all human studies in five domains: study population, selection and methods, outcome, analyses, and summary according to the Quality Appraisal Checklist—Quantitative Studies Reporting Correlations and Associations by the National Institute for Health Care Excellence (NICE) [34], as reported by Suba et al. [51] and further modified for this specific purpose (see Online Resource 3 for details). Finally, our results are reported according to PRISMA reporting guidelines for scoping reviews [58].

Results

We identified 3253 studies through database searches ending August 13, 2024. Following removal of 178 duplicates, two independent authors conducted title and abstract screening of a total of 3075 articles. Of these, 3027 articles were excluded. The main reasons for excluding articles were that the tissue in which the microdialysis catheter was placed did not meet our definition of healthy brain tissue, and that studies reported data from animals with non-gyrencephalic brains. Thus, 48 studies were selected for full-text screening, and three additional studies were identified through reference screening. After full-text screening, twelve studies were excluded. The main reason for exclusion at this stage was that the authors of the articles did not present data that were relevant for the present study in the publication, and did not provide these data after up to two attempts at contact (Fig. 1). Accordingly, a total of 39 studies were included in this review for data charting. Of this, six studies were on humans, 29 studies on pigs/swine, two studies on monkeys, one study on sheep, and one study on dogs.

Human studies

All six human studies were observational studies [1, 7, 24, 28, 47, 49]. One was conducted in patients diagnosed with non-lesional temporal lobe epilepsy [7], one in patients treated with temporal lobe resection for intractable epilepsy[24], one in patients with partial seizure during their assessment before neurosurgical treatment [1], one in patients treated for suspected malignant meningioma [28], one study included patients with acoustic neuroma, meningioma, or ependymoma [47], and the last study was conducted in patients with a posterior fossa or supratentorial lesion [49]. Three studies measured concentrations of biomarkers when the patients were awake [1, 7, 28] two studies measured biomarkers under anaesthesia and when patients were awake [47, 49], and one study measured the biomarker levels in some patients who were awake and in some patients during anaesthesia [24] (Online Resource 4). All studies used different combinations of equipment, see Table 2 for more details.

Four studies measured microdialysate concentrations of glucose [1, 28, 47, 49], three of lactate [1, 47, 49], two of pyruvate [47, 49], three of LPR [28, 47, 49], three of glycerol [28, 47, 49], and four of glutamate [7, 24, 28, 47]. One study measured all these biomarkers [47] (Table 3).

Individual human studies

Kanthan et al. [24] (1995) measured glutamate as well as other specific amino acids in five patients who underwent temporal lobe resection for severe epilepsy. Microdialysis was done in the temporal lobe during either neuroleptanalgesia or general anaesthesia before and after resection perfusing Ringer's solution at 2 μL min^{-1}. Values measured before resection were considered to represent baseline.

Reinstrup et al. [47] (2000) measured values of glucose, lactate, pyruvate, LPR, glutamate, and glycerol in nine patients before, during and after surgery for acoustic neuroma ($n=2$), meningioma ($n=6$), and ependymoma ($n=1$) in the posterior fossa. The microdialysate catheter was placed in healthy brain tissue in the frontal cerebral cortex and were perfused with Ringer solution at 1 μL min^{-1} two hours before surgery and immediately after anaesthesia, and at 0.3 μL min^{-1} six hours before or after anaesthesia. All reported values were considered to represent steady-state in healthy brain tissue. Glutamate levels were measured in four patients and were comparable at 1 μL min^{-1} in the anaesthetized state and at 0.3 μL min^{-1} in the awake state, but were somewhat lower at 1 μL min^{-1} in the awake state. Despite the lower perfusion rates, glutamate levels were slightly lower in this study than in the study by Kanthan et al. Glucose, lactate, pyruvate, and glycerol levels were higher at 0.3 μL min^{-1} in the awake state than at 1 μL min^{-1}

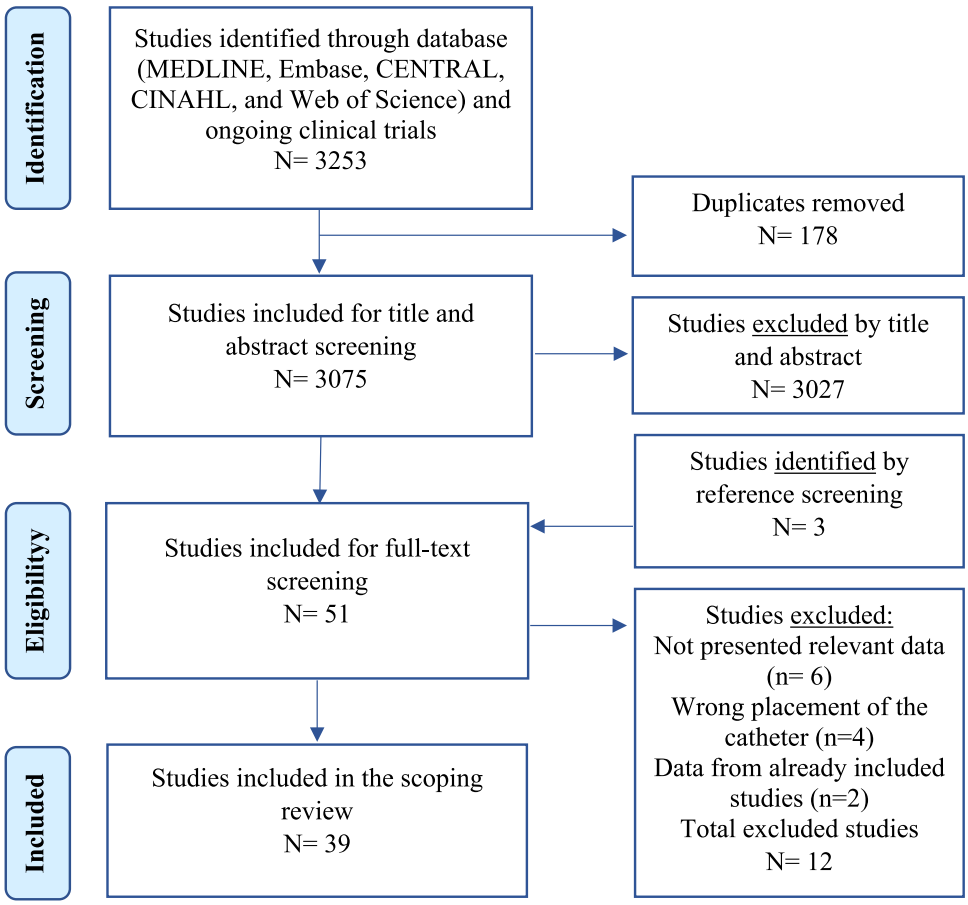

Fig. 1 Flowchart of the screening and selection process

in the anaesthetized state, whereas glutamate levels and LPR were unchanged.

Abi-Saab et al. [1] (2002) stereotactically placed a combined depth electrode and microdialysis catheter in twelve patients with complex partial seizures. The depth electrode was placed to localize the focus of the seizure disorder before neurosurgery. Measurements of glucose and lactate were obtained with microdialysis catheter perfused with sterile artificial extra cellular fluid, two to seven days after insertion. Microdialysis was performed in the awake state at 2.5 µL min^{-1} in six patients; in the other six patients the flow changed from 2.5 µL min^{-1} to 0.25 µL min^{-1}, and the basal level was reported using regression analysis to estimate values at a flow of zero (ZFM). All the measurements reported were from nonepileptic areas and were considered to represent measurements from healthy brain tissue. The zero-flow values of glucose and in particular lactate were higher than both values reported in the same study at 2.5 µL min^{-1} and those reported in awake patients by Reinstrup et al.; values reported at 2.5 µL min^{-1} were comparable to those reported in the awake state at 1 µL min^{-1} by Reinstrup et al.

Lindvall et al. [28] (2008) measured microdialysate values of glucose, LPR, glutamate, and glycerol in four patients with suspected malignant glioma who had undergone stereotactic biopsy or surgical resection, and in whom microdialysis catheters were inserted into or adjacent to the tumour or tumour cavity as well as in normal brain tissue. Microdialysis was performed at 1 µL min^{-1} in awake patients before and during air transportation at a cabin pressure corresponding to an altitude of 2500–3000 m. Values measured before air transportation in healthy brain tissue were considered to represent baseline. The glucose concentrations corresponded well to those reported by Reinstrup et al., also during wakefulness and also at 1 µL min^{-1}; however, LPR values were markedly higher, and glutamate levels were considerably lower.

Buchanan et al. [7] (2016) implanted a combined depth electrode and microdialysis catheter in the amygdala and the hippocampus of five patients with non-lesional temporal lobe epilepsy, who were asked to perform three specified sets of cognitive tasks. Microdialysis was conducted during the awake state at a flow of 5 µL min^{-1}; the type of perfusate was not specified. Glutamate levels measured at rest in between and after cognitive tasks were averaged to represent baseline and were slightly higher than those measured by Lindvall et al. at 1 µL min^{-1} in awake patients, but considerably lower than those measured by Kanthan et al. in sedated / anaesthetised patients at 2 µL

Table 2 Equipment and study design for the human studies

First author (year)	Catheter	MD catether pore size (kDa)	Equilibration time	Perfusion fluid	Perfusion rate (µL/min)	Analyzer
Kanthan [24] (1995)	Costum-made	ND	30 min	Sterile Ringer´s solution (pH approximate equals 6.7)	2	*Not described*
Reinstrup [47] (2000)	CMA 70, (CMA, Stockholm, Sweden, catheters)	20	*Not described*	Ringer solution (perfusion fluid; CMA Microdialysis)	1 / 0.3	CMA 600 microdialysis analyser
Abi-Saab [1] (2002)	Costum-made	ND	120 min	Sterile artificial ECF (147 mmol/L NaCl, 3 mmol/L KCl, 1.0 mmol/L MgCl2, 1.2 mmol/L CaCl2, 200 µmol/L ascorbate and a sodium phosphate buffer to pH 7.4)	2.5	High performance liquid chromatography (HPLC)
Lindvall [28] (2008)	CMA 70, (CMA, Stockholm, Sweden, catheters)	20	*Not described*	CSF perfusion fluid (Perfusion fluid CNS, CMA, Stockholm)	1	*Not described*
Buchanan [7] (2016)	Costum-made	ND	3–5 days	*Not described*	5	High performance liquid chromatography (HPLC) with an electrochemical detector
Sanchez-Guerrero [49] (2017)	CMA 71, (CMA, Stockholm, Sweden, catheters)	100	60 min	CNS perfusion fluid (M Dialysis AB) Sterile Isotonic CNS fluid	0.3	*Not described*

min^{-1} and Reinstrup et al. both in anaesthetised and awake patients at 1 or 0.3 µL min^{-1}.

Sánchez-Guerrero et al. [49] (2017) measured microdialysis values of glucose, lactate, pyruvate, LPR, and glycerol in 19 patients with posterior fossa lesions or supratentorial lesion both under anaesthesia and during wakefulness after surgery. The catheter was placed in the white matter of normal brain tissue and perfused with sterile isotonic cerebral fluid at a flow of 0.3 µL min^{-1} when the patient was awake. Under anaesthesia the flow was changed randomly between 0.1, 0.3, 0.6, 1.2, and 2.4 µL min^{-1} and the measurements obtained were analysed using ZFM. All reported microdialysis values were considered to represent measurements from healthy brain tissue. Both glucose, lactate, and pyruvate levels at 0.3 µL min^{-1} were markedly higher in the awake state than during anaesthesia, whereas the LPR was unchanged. Values measured in awake and anaesthetised patients, respectively, corresponded well to those reported by Reinstrup et al. in awake patients at 0.3 µL min^{-1} and in anaesthetised patients at 1 µL min^{-1}.

Animal studies

A total of 33 studies on gyrencephalic animals met the inclusion criteria. Of these, 29 studies were conducted in swine/pigs [2, 3, 6, 9–11, 13, 15, 20–22, 25, 26, 31, 32, 35–37, 39, 45, 46, 50, 52, 54, 55, 57, 60–62], two in monkeys [12, 14], one in sheep [53] and one in dogs[59]. In all studies, biomarkers were measured during general anaesthesia (Online Resource 2).

Seven studies measured both glucose, lactate, pyruvate, LPR, glutamate, and glycerol [3, 10, 11, 20, 31, 37, 61], four studies measured one of the biomarkers of interest [9, 14, 32, 59], and the rest of the studies ($n=22$) [2, 3, 6, 11, 12, 15, 20, 21, 25, 26, 31, 35, 36, 39, 46, 52, 54, 55, 57, 60–62] measured different combinations of the biomarkers (Table 4).

In the studies on swine/pigs, glucose measurements were reported in 21 out of 29 studies, lactate measurements were reported in 24 of the studies, pyruvate measurements were reported in 19 of the studies, LPR were reported in 18 of the studies, Glutamate measurements were reported in 15 of the studies, and glycerol measurements were reported in 17 of the studies.

Table 3 Measurements of biomarkers in normal brain tissue in human studies

First author (year)	N	MD catheter pore size (kDa) / flow rate (µL/min)	Localisation	Context	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (µmol/L):	Lactate/pyruvate ratio:	Glutamate (µmol/L):	Glycerol (µmol/L):
Kanthan [24] (1995)	5	ND / 2	Temporal lobe	Patients undergoing temporal lobe resection for epilepsy. Samples taken before resection Two patients underwent awake neuroleptic analgesia, three underwent general anaesthesia	-	-	-	-	20.22 ± 3.39 (mean ± SEM)	-
Reinstrup [47] (2000)	9	20 / 1 or 0.3	Frontal cerebral cortex	Anesthetized (1.0 µL/min)	1.2 ± 0.6	1.2 ± 0.6	70 ± 24	22 ± 6	17 ± 12	28 ± 16
				Awake, immediate postoperative (1.0 µL/min)	0.9 ± 0.6	1.4 ± 0.9	103 ± 50	21 ± 6	7 ± 5	42 ± 29
				Awake, 6 h before and after neurosurgery (0.3 µL/min))	1.7 ± 0.9	2.9 ± 0.9	166 ± 47	23 ± 4	16 ± 16	82 ± 44
Abi-Saab [1] (2002)	12	ND / 2.5 or ZFM	Localised epileptic focus Three in hippocamups, two in Heschls´s gyrus, one in thalamus, one in the parietal cotex. (One patient had two catheters in non-epileptic areas.)	Baseline from the hyperglycemic-hypoglycemic clamp study (2.5 µL/min) ($n = 6$ patients) (All patients awake)	0.82 ± 0.27	1.38 ± 1.2	-	-	-	-
				Baseline when using ZFM ($n = 6$ patients) (All patients awake)	1.57 ± 0.76	5.10 ± 1.37	-	-	-	-

Table 3 (continued)

First author (year)	N	MD catheter pore size (kDa) / flow rate (µL/min)	Localisation	Context	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (µmol/L):	Lactate/pyruvate ratio:	Glutamate (µmol/L):	Glycerol (µmol/L):
Lindvall [28] (2008)	4	20 / 1	Normal brain tissue. No further specifications	Fasting sample at 06:00 (All patients awake)	0.91 ± 0.26	-	-	45.18 ± 42.60	1.66 ± 0.70	16,830 ± 12,310
Buchanan [7] (2016)	5	ND / 5	Amygdala or hippocampus	Measurements from amygdala in awake patient under rest after a cognitive task	-	-	-	-	2.33 ± 1.97 (combined mean ± combined SD from three measurements)	-
				Measurement from hippocampus in awake patient under rest after a cognitive task	-	-	-	-	2.84 ± 2.43 (combined mean ± combined SD from three measurements)	-
Sanchez-Guerrero [49] (2017)	19	100 / ZFM or 0.3	In normal white matter. No further specifications	Anaesthesia, (ZFM)	1.57 (1.12 –4.70)	2.01 (1.37–5.44)	80 (53.9–223.3)	27.5 (14.9–39.5)	-	49.9 (21.7–228.7)
				Anaesthesia, (0.3 µL/min)	1.25 (0.64 –3.53)	1.40 (1.10–3.84)	73.8 (36.6–149.7)	23.3 (12.8–34.5)	-	53.8 (24.4–205.1)
				Awake, (0.3 µL/min)	1.55 (0.29 –3.01)	3.41 (1.56–5.62)	137.1 (85.0–192.0)	24.9 (16.9–35.1)	-	79.8 (29.3–346.4)

Values are mean ± standard deviation or median (range), unless otherwise specified

N Number of participants

MD Microdialysis

ND Not described

ZFM Zero flow method

Table 4 Measurements of biomarkers in normal brain tissue in animal studies

First autho (year)	n	How data and interval is expressed	Context	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (μmol/L)	Lactate/pyruvate ratio	Glutamate (μmol/L)	Glycerol (μmol/L)
Swine/pig									
Thoresen [56] (1998)	14	Mean +/- SE	Baseline at – 1, white matter	-	[c] 0.0183	1.92	10.84	-	-
			Baseline at – 1, grey matter	-	[c] 0.071 +/- 0.0129	7.41 +/- 1.83	11.19	-	-
Darling [8](2001)	24	Mean +/- SEM	Baseline	-	-	-	-	[d]3.43 +/- 1.14	-
Gardenfors [13] (2002)	32	Mean +/- SD	Control group (*n*=10)	1.8 +/- 0.8	1.8 +/- 0.8	92 +/- 31	21 +/- 9	11 +/- 6	28 +/- 10
Alessandri [2] (2003)	11	Mean +/- SEM	Baseline values sham group and trauma group , ipsilateral and contralateral	-	1.34 +/- 0.26 (combined mean +/- combined SEM from four groups)	46.4 +/- 16 (n=6)	32.81 +/- 12.07 (combined mean +/- combined SEM from four groups)	17.06 +/- 5.34 (combined mean +/- combined SEM from four groups)	-
Korth [26] (2003)	12	Mean +/- SD	Baseline	0.95 +/- 0.88	1.06 +/- 0.47	-	-	42.0 +/- 65.1	-
Van Hulst [16] (2003)	12	Mean +/- SD	Baseline at 0.4 FiO2	0.85 +/- 0.24	0.40 +/- 0.13	-	-	-	-
Munkeby [34] (2004)	69	Mean	Baseline group A (*n*=30) and group B (*n*=30)	-	-	-	-	-	13,23
Van Hulst [15] (2005)	11	Mean +/- SD	Baseline group A and group B	3.46 +/- 0.7 (combined mean +/- combined SD from two groups)	0.81 +/- 0.2 (combined mean +/-combined SD from two groups)	108.82 +/- 77.5 (combined mean +/- combined SD from two groups)	-	-	112.28 +/- 71.3 (combined mean +/-combined SD from two groups)
Henze [14] (2007)	10	Mean +/- SEM	Baseline	0.63 +/- 0.12	1.08 +/- 0.21	51.6 +/- 8.4	-	-	-
Meybohm [33] (2007)	18	Mean +/- SEM	Baseline	1.0 +/- 0.2	1.4 +/- 0.2	52 +/- 7	30 +/- 4	-	27 +/- 6

Table 4 (continued)

First autho (year)	n	How data and interval is expressed	Context	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (µmol/L)	Lactate/pyruvate ratio	Glutamate (µmol/L)	Glycerol (µmol/L)
Zoremba [62] (2007)	11	Mean +/- SEM	Control group (*n*=5) 15 samplings from this group	1.12 +/- 0.05 (combined mean +/- combined SEM from 15 samplings)	1.010.960.86 +/- 0.170.79 +/- 0.120.91 +/- 0.131.04 +/- 0.161.22 +/- 0.181.35 +/- 0.161.54 +/- 0.201.83 +/- 0.201.96 +/- 1.752.28 +/- 0.232.43 +/- 0.212.49 +/- 0.212.63 +/- 0.20	-	20.34 (combined mean from 15 samplings)	6.70 +/- 0.67 (combined mean +/- combined SEM from 15 samplings)	83.70+/- 3.93 (combined mean +/- combined SEM from 15 samplings)
Timaru-Kast [57] (2008)	34	Mean +/- SEM	Baseline, ipsilateral and contralateral, sham (*n*=11, ASDH 2ml (*n*=8), ASDH 5ml (*n*=8), and ASDH 9ml (*n*=3)	-	2.11 +/- 0.09 (combined mean +/- combined SEM from 8 samplings)	-	-	22.59 +/- 2.10 (combined mean +/- combined SEM from 8 samplings)	-
Bickenbach [6] (2009)	10	Mean +/- SD	Basline for bouth trial groups (HT and LT)	1.115 +/- 0.2111.193 +/- 0.303	1.333 +/- 0.1701.038 +/- 0.192	-	21.450 +/- 4.00826.985	-	-
Tovedal [59] (2010)	12	Mean +/- SD	SVC flow 100% (no obstruction, baseline) LQ: *n*=6, HQ: *n*=6	5.15 +/- 4.40 (combined mean +/- combined SD from two groups)	3.50 +/- 1,65 (combined mean +/- combined SD from two groups)	163.50 +/- 125.26 (combined mean +/- combined SD from two groups)	26.65 +/- 13.89 (combined mean +/- combined SD from two groups)	-	56.95+/- 42.27 (combined mean +/- combined SD from two groups)
Nielsen [37] (2011)	10	Mean +/- SD	Baseline "good side" (*n*=7), and "bad side" (*n*=7)	-	-	-	15 +/- 3.67 (combined mean +/- combined SD from two groups)	9 +/- 5.39 (combined mean +/- combined SD from two groups)	27 +/- 18.41 (combined mean +/- combined SD from two groups)
Purins [45] (2012)	6	Mean +/- SD	Baseline (*n*=5)	1.1 ± 0.5	0.9 ± 0.3	53.8 ± 15.5	17.7 ± 6.1	4.5 ± 1.3	27.4 ± 5.2

Table 4 (continued)

First autho (year)	n	How data and interval is expressed	Context	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (µmol/L)	Lactate/pyruvate ratio	Glutamate (µmol/L)	Glycerol (µmol/L)
Hwabejire [21] (2013)	10	Mean +/- SD	Baseline ipsilateral and contralateral, normal saline (*n*=5) and FFP (*n*=5)	-	0.662 +/- 0.346 (combined mean +/- combined SD from four groups)	24.480 +/- 22.023 (combined mean +/- combined SD from four groups)	-	80.617 +/- 49.154 (combined mean +/- combined SD from four groups)	29.456 +/−21.966(combined mean +/- combined SD from four groups)
Hwabejire [22] (2013)	9	Mean +/- SD	Baseline FFP (*n*=4) and FFP + VPA (*n*=5)	[a] 0.006 +/- 0.007 (combined mean +/- combined SD from two groups)	0.594+/−0.37 (combined mean +/- combined SD from two groups)	18.722 +/- 14.379 (combined mean +/- combined SD from two groups)	-	33.5 +/- 31.159 (combined mean +/- combined SD from two groups)	13.727 +/- 31.159 (combined mean +/- combined SD from two groups)
Nielsen [36] (2013)	10	Median (interquartile range)	Control group (*n*=3), right and left side	2.6 (2.0–2.9)	1.9 (1.1–2.1)	166 (96–226)	7 (6–11)	-	-
Nielsen [38] (2013)	11	Median (interquartile range)	Baseline for: contralateral (*n*= 5), Cyanide (*n*=5), NaCl (*n*=6)	2.4 (1.7–3.5)	1.2 (1.0–1.8)	104 (90–112)	9.5 (8–13)	9.5 (6.5–14)	22 (16–27)
Nyberg [40] (2014)	11	Median values with 25th–75th percentiles	Baseline	0.84 (0.51–1.13)	0.59 (0.51–1.13)	32.9 (22.2–50.9)	17.5 (13.3 −23.5)	-	-
Elvevoll [10] (2017)	12	Mean +/- SD	Baseline for DHCA (*n*=6) and DHLF (*n*=6)	-	-	-	16.36 +/- 6.33 (combined mean +/- combined SD from two groups)	-	44.135 +/- 18.466 (combined mean +/- combined SD from two groups)
Andelius [3] (2019)	10	Mean +/- 95% CI	Mean value every hour in the monitoring periode (20h) for 9 animals (*n*=9	0.79 +/- 0.42 (combined mean +/- 95% CI from 20 samplings)	1.53 +/- 0.11 (combined mean +/- 95% CI from 20 samplings)	81.14 +/- 7.49 (combined mean +/- 95% CI from 20 samplings)	-	-	45.81 +/- 55.46 (combined mean +/- 95% CI from 20 samplings)
Jakobsen [23] (2019)	10	Median (interquartile range)	Baseline	2.2 (1.8–3.0)	2.3 (1.3–3.0)	[b]142 000 (98000–203000)	13 (8–16)	15 (4–22)	38 (25–88)
Kurtz [27] (2019)	12	Mean +/- SD	Baseline: sepsis group (*n*=7) control group (*n*=5)	1.988 +/- 0.59 (combined mean +/- combined SD from two groups)	-	[b] 138 472 +/−23 570 (combined mean +/- combined SD from two groups)	22.83 +/- 4.44 (combined mean +/- combined SD from two groups)	102.42 +/- 40.17 (combined mean +/- combined SD from two groups)	527. 30 +/- 144.48 (combined mean +/- combined SD from two groups)

Table 4 (continued)

First autho (year)	n	How data and interval is expressed	Context	Glucose (mmol/L)	Lactate (mmol/L)	Pyruvate (µmol/L)	Lactate/pyruvate ratio	Glutamate (µmol/L)	Glycerol (µmol/L)
Putzer [46] (2021)	14	Median (25th to 75th percentile) with estimated difference	Baseline	[e]0.6 (0.3–0.7)	[e]1 (0.5–1.6)	[d]43 (32–64)	30 (13–38)	-	-
Schiefecker [52] (2021)	8	Median and inter-quartile range (IQR)	Baseline	[e]0.5 (0.1–0.8)	[e]1.4 (0.6–2.4)	[d]41 (25–48)	38 (13–56)	[d]46 (5–85)	[f]57000 (43000–63000)
Donadello [9] (2022)	15	Mean +/- SD	Baseline normothermia (n=5), hypothermia (n=5), hypothermia with controlled oxygenation (n=5)	2.94 +/- 1.27 (combined mean +/- calculated SD for all three groups)	4.11 +/−1.74 (combined mean +/- calculated SD for all three groups)	187.67 +/- 56.04 (combined mean +/- calculated SD for all three groups)	19.43 +/- 4.96 (combined mean +/- calculated SD for all three groups)	70.33 +/- 39.05 (combined mean +/- calculated SD for all three groups)	68.33 +/- 28.51 (combined mean +/- calculated SD for all three groups)
Svedung Wettervik [54] (2024)	4	Mean	Baseline form two samplings	846 (combined mean from two samplings)	794 (combined mean from two samplings)				
Monkeys									
Galvan [12] (2003)	2	Mean +/- SEM	Average basal level	-	-	-	-	[d]28.74 +/- 2.73	-
Frykholm [11] (2001)	8	Mean +/- SD	Baseline: Severe ischaemia probe region with reperfusion (n=8), region with no reperfusion (n=8), and penumbra (n=5)	-	-	-	20.56	2.49	2.70
Sheep									
Taccone [55] (2014)	15	Mean +/- SD	Baseline sham group (n=5) and sepsis group (n=10)	1.335+/- 0.069	1.2168 (+/- 0.526) (only measured in sham group)	62.0192 (+/- 21.786) (only measured in sham group)	21.373 +/−3.058 (combined mean +/- combined SD from two groups)	[b]9700 (combined mean from two groups)	14.96 +/- 3.411 (combined mean +/- combined SD from two groups)
Dogs									
Tseng [61] (1999)	10	Mean +/- SD	Baseline	-	-	-	-	2.4 +/- 1.9	-

[a]Converted from mg/dL,[b]Converted from mmol/L[c]Converted from µmol/L, [d]Measurement reported in µmol[e]Measurements reported in mmol, [f]Measurements reported in mmol and converted to µmol

One study on monkeys reported measurements of LPR, glutamate, and glycerol[12], the other study on monkeys reported measurements of only glutamate[14].

One study on sheep[53] measured glucose, lactate, pyruvate, LPR, glutamate, and glycerol. One study on dogs[59] reported only measurements of glutamate.

Critical appraisal of human studies

None of the included studies had a pre-published protocol. All the included studies[1, 7, 24, 28, 47, 49] were non-blinded observational studies; no randomized trials were identified. All the included human studies have been critical appraised using five domains; study population, selection and methods, outcome, analyses, and summary (Table 5., Online Resource 3). Overall, four studies[1, 7, 24, 28] were downgraded because the study population was poorly defined. Furthermore, two[24, 47] were downgraded because the methods were incompletely described, and four[1, 24, 28, 47] were downgraded because analyses were unclear. All the included studies were downgraded to a single plus in the summary domain because the findings were not perceived as fully generalizable to healthy human tissue.

Discussion

This scoping review showed that the studies measuring normal values of common biomarkers were heterogeneous. There was low generalizability of method, study population, and findings.

We expected heterogeneity between studies, and therefore chose to conduct a scoping review of the field to identify and analyse potential knowledge gaps. A methodologically stringent process was followed, with a prespecified protocol, searching relevant databases, and having two authors screen title, abstract and full-text independently of each other. Our search strategy was broad, which complicated the screening process, but minimised the risk of missing important studies. To minimise the risk even more, we searched for ongoing clinical trials before finishing the review. We included studies on both humans and gyrencephalic animals, thus providing an overview over all published studies that have measured values of common biomarkers with cerebral microdialysis in presumably healthy brain tissue.

Even so, this review also has limitations. A very specific limitation of this review is the definition of healthy brain tissue. On one hand, due to ethical considerations, we expected to find no reports of cerebral microdialysis conducted in healthy humans and therefore chose to include patients with focal brain tissue lesions, in whom measurements were done outside these lesions. On the other hand, focal brain tissue may affect the brain globally. A strict definition was established in our protocol to minimize the risk of including data from trials measuring values in tissue that we perceived not to represent healthy brain tissue. However, the definition can be debated and may lead to missing data from excluded studies. Thus, Langemann et al.[27] (2002) published a study where they inserted a microdialysis catheter distant from the resection during tumour operations, Bergenheim et al. [5] (2006) placed a microdialysis catheter 0–25 mm from the tumour margin, and Roslin et al.[48] (2003) placed the catheter 10 mm from a contrast-enhancing tumour; all three studies were excluded from this review because the catheter was placed in the ipsilateral hemisphere and close to the tumour.

Table 5. Summary of critical appraisal of the human studies on five domains

Well covered (overweight of ++)						🟢
Partly covered (overweight of +)						🟡
Not covered at all or poorly covered (Overweight of -/nd)						🔴
	Kanthan (1995)	Reinstrup (2000)	Abi-Saab (2002)	Lindvall (2008)	Buchanan (2016)	Sanchez-Guerrero (2017)
1. Population	🔴	🟢	🔴	🔴	🔴	🟢
2. Selection/Methods	🔴	🟡	🟢	🟢	🟢	🟢
3. Outcomes	🟢	🟢	🟢	🟢	🟢	🟢
4. Analyses	🔴	🟡	🟡	🔴	🟢	🟢
5. Summary	🟡	🟡	🟡	🟡	🟡	🟡

*If the study was rated with equal amounts of ++/+/-/ND in the critical appraisal, the colour in the summary table shows the lowest rating

Intracerebral microdialysate values likely vary by anatomical site, e.g. white or grey matter, state of wakefulness or anaesthesia, and administration of drugs such as anaesthetics and other psychotropic agents. This multifactorial issue makes studies valuable in which repeated measurements are done with careful variation of one factor at a time. One particularly important question is how microdialysate varies by anaesthesia vs. wakefulness. Two of the human studies reported here[47, 49] conducted microdialysis both during anaesthesia and wakefulness. While the point estimates at least for lactate and pyruvate increased in both studies in the awake compared to the anaesthetised state, the point estimate for glucose decreased slightly in one study[47] and increased slightly in another[49]. As Reinstrup et al. placed the microdialysis probe in the frontal cortex, compared to the white matter used by Guerrero-Sanches et al., and as Reinstrup et al. also varied the microdialysis perfusion rate during the study and did not report values during anaesthesia at 0.3 µL min^{-1}, the studies are not easily comparable. However, one safe conclusion across the six human studies appears to be that the LPR was quite robust towards change in anaesthesia level as well as perfusion rates; only one study[28] stood out with markedly different LPR values that were about twice as high as in the remaining studies.

In the studies with gyrencephalic animals, we mainly looked at the reported baseline value instead of the outcome. The studies presented limited information about the process when measuring baseline values, which rendered the studies less comparable to each other. Importantly, the animal studies were all done in anaesthetised animals for ethical reasons, and therefore provided no information on the effect of anaesthesia in itself compared to the awake state.

Also, the results in the various studies in both humans and animals have originally been presented in different units, now converted into comparable units to make a direct comparison possible. Reported measurements that were comparable were combined in Tables 3 and 4.

Normal values of glucose, lactate, pyruvate, LP-ratio, glutamate and glycerol

To our knowledge, this is the first review that collects the current knowledge of normal values of common biomarkers in cerebral microdialysate. In current neurointensive care, relative changes are used more commonly than absolute values to guide treatment. However, the consensus statement from the 2014[18] also defined low glucose as levels of glucose under 0.8 mmol/L, high lactate as levels over 4 mmol/L, and high lactate/pyruvate ratio as levels over 25 or 40. In some of the human studies reported here, the confidence interval included values that differed from the consensus values.

The animal studies[2, 3, 6, 9–15, 20–22, 25, 26, 31, 32, 35–37, 39, 45, 46, 50, 52–55, 57, 59–62] reported a wider range of measured values than the human studies[1, 7, 24, 28, 47, 49], except for two biomarkers. Thus, the reported mean values for glycerol in the human studies ($n = 2$) [28, 47] were from 28–16,830 µmol/L, while in the animal studies ($n = 16$)[3, 10–13, 20, 21, 26, 31, 32, 35, 45, 53, 57, 61, 62] a smaller, though still substantial range of mean values from 1.03–397 µmol/L were reported. Also, the reported median measurements of lactate in one human study[49] were 1.40–3.41 mmol/L, while the reported median values of lactate in six animal studies[22, 36, 37, 39, 46, 50] (all on pigs) ranged from 0.59 – 2.30 mmol/L. However, it was not possible to derive normal values of the biomarkers, based on the animal studies.

Heterogeneity

In the six studies on humans[1, 7, 24, 28, 47, 49], the clinical and methodological heterogeneity was noticeable. Three different microdialysis catheters were used, the catheters were placed in different locations in the human brain and widely different diagnoses were studied. Furthermore, the perfusion rate varied, and some used the zero-flow method to calculate the value. This was also the case with the included animal studies, which reported the use of 14 different catheters. The relative recovery changes both according to the catheter design and perfusion rate, with larger pore sizes, longer membranes, and slower perfusion rates leading to higher recovery and, in effect, higher biomarker values. This has been shown both in patients with severe acute brain injury[16] and in the study by Reinstrup in healthy brain tissue of patients undergoing neurosurgery[47], whereas the lactate-pyruvate ratio remained unchanged. This heterogeneity makes it difficult to compare the reported values.

Another noticeable difference between the studies was the time from insertion of the microdialysis catheter to baseline sampling. This time, also called the equivalence period, varied from zero to 12 h in the human studies, and from zero to 20 h in the animal studies. Andelius et al.[3] have reported that the insertion of a microdialysis catheter into the parenchyma, always results in a minor trauma, and sufficient equilibration time is important to get valid baseline values. The time needed to establish steady state varied depending on the perfusion rate and differed between the different biomarkers that were measured.

Critical appraisal was done on all the human studies [1, 7, 24, 28, 47, 49], and we reported a number of design or reporting problems (Table 5., Online Resource 3). The main problem in four of the studies[1, 7, 24, 28] was the

insufficient description of the population selection process. There was no description of inclusion or exclusion criteria, and it was not possible to appraise whether the patient population represented the eligible population. Furthermore, Kanthan et al.[24] had problems in all the appraised domains, and the study was overall downgraded on four out of five domains in the summary Table 5.. Sanchez-Guerrero et al.[49] had only problems in three of the domains, and in the summary the study was only downgraded in one out of five domains. This demonstrates room for improvement in the quality of the studies. In the summary domain, all the studies were downgraded because of placement of the probe in presumably healthy brain tissue, and as discussed earlier, this is a limitation in all the studies, thus also in this scoping review. However, intracerebral microdialysis should still be considered an advanced technology; the studies here should be considered pioneering endeavours towards a more thorough understanding of the technique, which may hopefully lead to further harmonization in the future.

Conclusion

This scoping review identified studies that measured commonly used biomarkers in healthy brain tissue by intracerebral microdialysis, and described heterogeneity between the measured values, the equipment used in the studies, their methodology and results. To our knowledge, this was the first systematic literature review describing normal values of common biomarkers in humans and gyrencephalic animals. We found six studies on humans and 33 studies on gyrencephalic animals, all using different methods. Our findings uncover a knowledge gap in this field. In order to gain further insight, more standardized methods when analysing biomarkers with cerebral microdialysis are needed to provide comparable measurements. Studies in different anatomical parts of the brain, and in awake and sedated state are necessary to fully understand the normal energy metabolism in the healthy brain tissue. For ethical reasons, studies on healthy human individuals are not possible. Therefore, studies on patients undergoing surgery for focal brain injuries and where a microdialysate catheter at a safe distance from the affected side, such as in the contralateral hemisphere, would be relevant in the future.

Authors´contributions.

ILG, HRJ and MLF screened articles for title, abstract and full text, and any discrepancy was solved by consulting MKS. All authors agreed on the data charting form and ILG, HRJ and MLF charted data. Any discrepancy was discussed and solved with agreement of all authors. KM modified the critical appraisal form. ILG wrote the main manuscript text and prepared figures and tables. All authors reviewed the manuscript for important intellectual content and contributed to the revision process.

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Declarations

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