



SYSTEMATIC REVIEW PROTOCOL FOR ANIMAL INTERVENTION STUDIES

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VERSION 2.0 (DECEMBER 2014)

Item #	Section/Subsection/Item	Description	Check for approval
A. General			
1.	Title of the review	Amino acids in microdialysates	
2.	Authors (names, affiliations, contributions)	Cathalijn H.C. Leenaars Judith van Luijk Jennifer Freymann Thomas J. van Ee Bea Zoer Pim Drinkenburg Rob B.M. de Vries	
3.	Other contributors (names, affiliations, contributions)	Sophie Jansen and A. Offens are kindly acknowledged for providing assistance in protocol development.	
4.	Contact person + e-mail address	Cathalijn.Leenaars@radboudumc.nl	
5.	Funding sources/sponsors	ZonMW	
6.	Conflicts of interest	None	
7.	Date and location of protocol registration	12-JAN-2017 SYRCLE website	
8.	Registration number (if applicable)	-	
9.	Stage of review at time of registration	Searches in progress	
B. Objectives			
Background			
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	<p>Since its development in the 1980's, microdialysis has widely been used for <i>in vivo</i> measurement of neurotransmitters and neuromodulators at the locations where they are present.¹</p> <p>Amino acids are not only the building blocks of proteins, but can also function as excitatory (e.g. Glu and Asp) and inhibitory (GABA) neurotransmitters, and have habitually been measured with microdialysis in several regions of the brain. Preceding narrative reviews have e.g. analysed the neuronal vs. glial origin of Glu and GABA in dialysates², or described the effects of anaesthesia on several amino acids in dialysates³.</p> <p>Microdialysis concentration measurements heavily depend on experimental factors such as the perfusion fluid running speed, the used membrane and the region of interest. Methods vary between research groups, which may result in differences in baseline values.</p> <p>To date, no systematic review of the microdialysis technique has been published. This systematic review will map all published baseline amino acid concentrations in dialysate for the selected amino acids, and explore variability within and between research groups.</p>	
Research question			
11.	Specify the disease/health problem of interest	Any (no restrictions)	
12.	Specify the population/species studied	All non-human animals	

		dialysate	
27.	Language restrictions	Inclusion criteria: Any Exclusion criteria: -	
28.	Publication date restrictions	Inclusion criteria: Any Exclusion criteria: -	
29.	Other	Inclusion criteria: - Exclusion criteria: -	
30.	Sort and prioritize your exclusion criteria per selection phase	<p><u>Selection phase: Screening title/abstract</u></p> <ol style="list-style-type: none"> 1. No microdialysis 2. Extracerebral dialysis 3. Human & in vitro studies 4. None of the selected amino acids measured in dialysate (asparagine AND/OR aspartate AND/OR GABA AND/OR glutamate AND/OR glutamine AND/OR glycine AND/OR histamine AND/OR proline AND/OR taurine) <p><u>Selection phase: Full text</u></p> <ol style="list-style-type: none"> 1. No primary study or review without new data 2. No microdialysis 3. Extracerebral 4. Human & in vitro studies 5. None of the selected amino acids measured 	
Study characteristics to be extracted (for assessment of external validity, reporting quality)			
31.	Study ID (e.g. authors, year)	<ul style="list-style-type: none"> - Authors - Year - Title - Journal - Language - Research group - Laboratory location 	
32.	Study design characteristics (e.g. experimental groups, number of animals)	<ul style="list-style-type: none"> - Number of animals 	
33.	Animal model characteristics (e.g. species, gender, disease induction)	<ul style="list-style-type: none"> - Animal species/strains - Age/weight - Sex 	
34.	Intervention characteristics (e.g. intervention, timing, duration)	<ul style="list-style-type: none"> - Flow rate - Probe length - Probe / membrane type - Probe location (brain area) - Re-use of probe or animal - Washout time - Baseline measurement time - Type of anaesthesia/freely behaving 	
35.	Outcome measures	Baseline concentration of the amino acids asparagine, aspartate, GABA, glutamate, glutamine, glycine, histamine, proline and taurine in dialysates (nmol/ml; refer to 39)	
36.	Other (e.g. drop-outs)	-	
Assessment risk of bias (internal validity) or study quality			
37.	Specify (a) the number of reviewers assessing the risk of bias/study quality	(a) 1 reviewer; a random sample of approximately 5% of the included studies will be checked by a second	

	in each study and (b) how discrepancies will be resolved	reviewer. (b) Discussion between reviewers	
38.	Define criteria to assess (a) the internal validity of included studies (e.g. selection, performance, detection and attrition bias) and/or (b) other study quality measures (e.g. reporting quality, power)	<input type="checkbox"/> By use of SYRCLE's Risk of Bias tool⁴ <input type="checkbox"/> By use of SYRCLE's Risk of Bias tool, adapted as follows: <input type="checkbox"/> By use of CAMARADES' study quality checklist, e.g.²² <input type="checkbox"/> By use of CAMARADES' study quality checklist, adapted as follows: <input checked="" type="checkbox"/> Other criteria, namely: Extracted study characteristics (31-35) will be tabulated. This information (or lack of it) provides an indication of study quality, internal validity and risk of bias. (The available risk of bias tools are hardly applicable to baseline measurements.)	
Collection of outcome data			
39.	For each outcome measure, define the type of data to be extracted (e.g. continuous/dichotomous, unit of measurement)	Baseline concentration of the amino acids asparagine, aspartate, GABA, glutamate, glutamine, glycine, histamine, proline and taurine in dialysates in nmol/ml. Where needed, concentration units will be converted.	
40.	Methods for data extraction/retrieval (e.g. first extraction from graphs using a digital screen ruler, then contacting authors)	<ul style="list-style-type: none"> • Data extraction from tables and text • If only graphical data is available, digital image software will be used to obtain these data 	
41.	Specify (a) the number of reviewers extracting data and (b) how discrepancies will be resolved	a) 1 reviewer; a random sample of approximately 5% of the included studies will be checked by a second reviewer. b) Discussion between reviewers	
Data analysis/synthesis			
42.	Specify (per outcome measure) how you are planning to combine/compare the data (e.g. descriptive summary, meta-analysis)	Results will be tabulated, grouped by laboratory. No meta-analysis is planned.	
Final approval by (names, affiliations):		Cathalijn Leenaars (SYRCLE) Rob de Vries (SYRCLE)	Date:12-JAN-2017

References:

1. Anderzhanova E and Wotjak CT. Brain microdialysis and its applications in experimental neurochemistry. Cell and tissue research, 2013. 354(1):27-39.
2. Westerink BHC, Rea K, Oldenziel WH, Cremers TIFH. Microdialysis of glutamate and GABA in the brain: analysis and interpretation. 2007. Handbook of microdialysis 16:17-31.
3. De Souza Silva MA, Müller CP, Huston JP. Microdialysis in the brain of anesthetized vs. freely moving animals. 2007. Handbook of microdialysis 16: 71-91.

Search strategy:

PubMed

Amino Acids

Amino Acids[MeSH] OR ((Amino[tiab] OR Aminergic[tiab]) AND (Acid[tiab]OR Acids[tiab])) OR

Asparagine

Asparagine[MeSH] OR Asparagine*[tiab] OR Asn[tiab] OR (carbamoylpropanoic AND (Acid[tiab] OR Acids[tiab])) OR

Aspartate

Aspartic Acid[MeSH] OR Aspart*[tiab] OR ((Aspar*[tiab] OR aminosuccinic[tiab]) AND (Acid[tiab] OR Acids[tiab])) OR Asp[tiab] OR

GABA

gamma-Aminobutyric Acid[MeSH] OR GABA[tiab] OR ((Aminobut*[tiab] OR Butanoic[tiab] OR Butyric[tiab]) AND (Acid[tiab] OR Acids[tiab])) OR

Glutamate

Glutamic Acid[MeSH] OR Glutamate[tiab] OR Glu[tiab] OR ((Glutamic[tiab]OR Glutaric[tiab]OR Aminopentanedioic[tiab]) AND (Acid[tiab] OR Acids[tiab])) OR

Glutamine

Glutamine[MeSH] OR Glutamine[tiab] OR Gln[tiab] OR (carbamoylbutanoic[tiab] AND (Acid[tiab] OR Acids[tiab])) OR

Glycine

Glycine[MeSH] OR Glycine*[tiab] OR Gly[tiab] OR (Aminoacetic[tiab] AND (Acid[tiab] OR Acids[tiab])) OR glycocoll[tiab] OR

Histamine

Histamine[MeSH] OR Histamine [tiab] OR His[tiab] OR ethanamine[tiab] OR Histidine[tiab] OR

Proline

Proline[MeSH] OR Proline[tiab] OR Pro[tiab] OR

Taurine

Taurine[MeSH] OR Taurine[tiab] OR Tau[tiab] OR ((Tauric[tiab] OR aminoethanesulfonic[tiab] OR aminoethane[tiab]) AND (Acid[tiab] OR Acids[tiab])) AND

Microdialysis

microdialysis[MeSH] OR micro dial*[tiab] OR microdial*[tiab] OR microD[tiab] OR chemitrode[tiab] OR dialytrode[tiab] OR brain dialys*[tiab] OR intracerebral dialys*[tiab] OR cerebral dialys*[tiab] OR intracranial dialys*[tiab] OR cranial dialys*[tiab] OR transcranial dialys* [tiab]

AND the **SYRCLE animal filter** (Hooijmans, C.R., et al., Enhancing search efficiency by means of a search filter for finding all studies on animal experimentation in PubMed. Laboratory animals, 2010. 44(3): p. 170-175.)

Embase

Amino Acids

amino Acid/ OR ((Amino OR Aminergic)AND (Acid OR Acids)).ti,ab,kw. OR

Asparagine

asparagine/ OR (Asparagine* OR Asn OR (carbamoylpropanoic AND (Acid OR Acids))).ti,ab,kw. OR

Aspartate

aspartic Acid/ OR (Aspart* OR ((Aspar* OR Aminosuccinic) AND (Acid OR Acids)) OR Asp).ti,ab,kw. OR

GABA

4 aminobutyric Acid/ OR GABA.ti,ab,kw. OR ((Aminobut* OR Butanoic OR Butyric) AND (Acid OR Acids)).ti,ab,kw. OR

Glutamate

glutamic Acid/ OR Glutamate.ti,ab,kw. OR Glu.ti,ab,kw. OR ((Glutamic OR Glutaric OR Aminopentanedioic) AND (Acid OR Acids)).ti,ab,kw. OR

Glutamine

glutamine/ OR (glutamine OR Gln OR (carbamoylbutanoic AND (Acid OR Acids))).ti,ab,kw. OR

Glycine

glycine/ OR (Glycine* OR Gly OR (Aminoacetic AND Acid) OR glycoll).ti,ab,kw. OR
Histamine

histamine/ OR (Histamine OR His OR ethanamine OR Histidine).ti,ab,kw. OR

Proline

proline/ OR (Proline OR Pro).ti,ab,kw. OR

Taurine

taurine/ OR (Taurine OR Tau OR ((Tauric OR aminoethanesulfonic OR aminoethane) AND (Acid OR Acids))).ti,ab,kw. AND

Microdialysis

microdialysis/ OR (micro dial* OR microdial* OR microD OR chemitrode OR dialyetrode OR brain dialys* OR intracerebral dialys* OR cerebral dialys* OR intracranial dialys* OR cranial dialys* OR transcranial dialys*).ti,ab,kw.

AND the **SYRCLE animal filter** (de Vries, R., et al., Updated version of the Embase search filter for animal studies. 2014.)