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	Adenosine concentrations in microdialysates	
2.	Authors (names, affiliations, contributions)	S. van der Mierden S. Savelyev R. de Vries C.H.C. Leenaars	
3.	Other contributors (names, affiliations, contributions)		
4.	Contact person + e-mail address	Dr. H.C. Leenaars, cathalijn.leenaars@radboudumc.nl	
5.	Funding sources/sponsors		
6.	Conflicts of interest	None	
7.	Date and location of protocol registration		
8.	Registration number (if applicable)		
9.	Stage of review at time of registration	Searching in progress	
	B. Objectives		
	Background		
10.	What is already known about this disease/model/intervention? Why is it important to do this review?	Since it development in the 80's microdialysis has proven a useful technique for *in vivo* measurements of small molecules like neurotransmitters and neuromodulators measuring these molecules at the locations where they are present [1] A neuromodulator analysed using this technique is adenosine (and its derivatives like AMP, ADP etc.). Adenosine is best known for its involvement in sleep [2]. Over the years multiple studies have measured the concentrations of adenosine in different parts of the brain under different circumstances. The measured concentrations vary however due to differences between studies, like the species and strains of animals used, but also due to differences like the flow rate or diameter of the microdialysis probe. A systematic review can give an overview of the differences and will provide a base for future studies involving adenosine.	
	Research question		
11.	Specify the disease/health problem of interest	-	
12.	Specify the population/species studied	All animals	
13.	Specify the intervention/exposure	Sleep deprivation, administration of any compound, other interventions or no intervention	
14.	Specify the control population	Any	
15.	Specify the outcome measures	Adenosine & AMP concentrations in intracerebral	

		microdialysate	
16.	State your research question (based on items 11-15)	What is the reported range of concentrations of adenosine and AMP in intracerebral microdialysates.	
	C. Methods		
	Search and study identification		
17.	Identify literature databases to search (*e.g.* Pubmed, Embase, Web of science)	**X** MEDLINE via PubMed **X** Web of Science ☐SCOPUS **X** EMBASE ☐Other, namely: ☐Specific journal(s), namely:	
18.	Define electronic search strategies (*e.g.* use the step by step search guide[15] and animal search filters[20, 21])	Search strategies provided below.	
19.	Identify other sources for study identification	**X** Reference lists of included studies ☐Books **X** Reference lists of relevant reviews ☐Conference proceedings, namely: ☐Contacting authors/ organisations, namely: ☐Other, namely:	
20.	Define search strategy for these other sources	Check if references meet the inclusion criteria and have already been retrieved. Add new references that meet the inclusion criteria.	
	Study selection		
21.	Define screening phases (*e.g.* pre-screening based on title/abstract, full text screening, both)	Both Title/abstract screening and full text screening.	
22.	Specify (a) the number of reviewers per screening phase and (b) how discrepancies will be resolved	(A) Two reviewers per screening phase (using EROS) (B) Discussion until concession is reached	
	Define all inclusion and exclusion criteria based on:		
23.	Type of study (design)	Inclusion criteria: Primary study Exclusion criteria: Review not including new data	
24.	Type of animals/population (*e.g.* age, gender, disease model)	Inclusion criteria: any animal Exclusion criteria: human study, in vitro study	
25.	Type of intervention (*e.g.* dosage, timing, frequency)	Inclusion criteria: Intracerebral microdialysis Exclusion criteria: Extracerebral, no microdialysis	
26.	Outcome measures	Inclusion criteria: Adenosine AND/OR AMP measured Exclusion criteria: No adenosine OR AMP measured	
27.	Language restrictions	Inclusion criteria: Any Exclusion criteria: -	
28.	Publication date restrictions	Inclusion criteria: All data found Exclusion criteria: -	
29.	Other	Inclusion criteria: Exclusion criteria:	
30.	Sort and prioritize your exclusion criteria per selection phase	Selection phase: screening title/abstract 1. No microdialysis 2. Certainly no adenosine or AMP 3. Extracerebral 4. human & in vitro studies	

		Selection phase: full text 1. No microdialysis 2. No adenosine or AMP 3. Extracerebral 4. No primary study or review without new data 5. Human & in vitro studies	
**Study characteristics to be extracted (for assessment of external validity, reporting quality)**
31.	Study ID (*e.g.* authors, year)	- Authors, - Year, - Title, - Journal, - Language	
32.	Study design characteristics (*e.g.* experimental groups, number of animals)	- Number of animals	
33.	Animal model characteristics (*e.g.* species, gender, disease induction)	- Animal species/strains, - Age/weight, - Sex, - Housing, - Day/night cycle (gradual/abrupt change, type of lighting, time of lights on/off)	
34.	Intervention characteristics (*e.g.* intervention, timing, duration)	- Flow rate, - Probe diameter, - Probe length, - Microdialysis membrane (properties), - Dialysis probe location, - Detection method (type of HPLC + type of detection), - Washout time/baseline measurement time, - Type of anaesthesia/freely behaving, - Measurement bin times, - Total measurement times, - Clock-time of measurements	
35.	Outcome measures	Adenosine & AMP Concentration (nmol/ml; see 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 in each study and (b) how discrepancies will be resolved	(a) 1 reviewer (see 38, 41)	
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)	☐By use of SYRCLE's Risk of Bias tool ☐By use of SYRCLE's Risk of Bias tool, adapted as follows: ☐By use of CAMARADES' study quality checklist, e.g [22] ☐By use of CAMARADES' study quality checklist, adapted as follows: X Other criteria, namely: Extracted study characteristics (point 31-35) will be tabulated. This information (or lack of it) provides an indication of study quality, internal validity	

		and risk of bias. As this is a method-focussed SR, no formal risk of bias will be done.	
	Collection of outcome data		
39.	For each outcome measure, define the type of data to be extracted (*e.g.* continuous/dichotomous, unit of measurement)	Adenosine & AMP: concentration (nmol/ml; other units will be converted and the original unit will also be reported)	
40.	Methods for data extraction/retrieval (*e.g.* first extraction from graphs using a digital screen ruler, then contacting authors)	1. Data extraction from table and text 2. 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 sample of 5% will be checked for consistency by a second reviewer	
	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. We consider performing meta-analyses on the effects of sleep deprivation and / or microdialysis methodology on adenosine concentrations if enough data is available.	
Final approval by (names, affiliations):		C.H.C. Leenaars, S. vd Mierden (SYRCLE) Date: 25/01/2016	

References

Search strategies:
Pubmed:

adenosine[mesh] OR adenosine[tiab]

OR adenosine monophosphate[mesh] OR (AMP[tiab] OR (adenylic acid[tiab]))

AND (Microdialysis[mesh] OR microdialysis[tiab] OR (micro dial*[tiab]) OR microdial*[tiab] OR (micro dialyz*) or microdialyz*[tiab] OR microD[tiab])

AND SYRCLE animal filter [3]

Embase:
adenosine/ or (adenosin or adenosine).ti,ab,kw.

OR adenosine phosphate/ or (amp or adenylic acid).ti,ab,kw.

AND exp microdialysis/ OR (microdial* OR micro dial* OR microD).ti,ab,kw.

AND SYRCLE animal filter [4]

Web of Science:

TS=(adenosine) OR TS=(adenosin*)

OR TS=(AMP) OR TS=(adenylic acid)

AND TS=(microdialy*) OR TS=(micro dial*) OR TS=(microD)

1. Anderzhanova, E. and C.T. Wotjak, *Brain microdialysis and its applications in experimental neurochemistry.* Cell and tissue research, 2013. **354**(1): p. 27-39.
2. Porkka-Heiskanen, T. and A.V. Kalinchuk, *Adenosine, energy metabolism and sleep homeostasis.* Sleep Medicine Reviews, 2010. **15**(2): p. 123-135.
3. 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.
4. de Vries, R., et al., *Updated version of the Embase search filter for animal studies.* 2014.