CAMARADES Monograph No. 7

A Systematic Approach to Research Synthesis for the Pathophysiology of Stroke

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Contents:

A Systematic Approach to Research Synthesis for the Pathophysiology of Stroke

1. Abstract:

Background/Objective: Stroke has been researched for over 20 years and more than 1000 neuroprotective interventions have been investigated[1]. An understanding of the pathophysiology of stroke is crucial to the identification of steps to be targeted in the ischemic cascade. *Methods:* Systematic review of papers describing the use of the NMDA receptor antagonist MK801 in vivo or in vitro in models of stroke. DerSimion and Laird random effects meta-analysis. *Results:* 381 experiments were identified. Mean study quality was 3.4/11 with a range of 2-6. 45 experiments reported MK801 in middle cerebral artery occlusion (MCAO) to reduce infarct volume by 26.3% (95% CI 20.6%-32%, $p < 0.001$). 24 experiments reported MK801 in excitotoxic lesion to reduce lesion volume by 55.9% (95% CI 43.6%-68.1%, $p<0.001$). *Conclusion:* MK801 demonstrates a degree of neuroprotective efficacy in experimental stroke. We demonstrate how study quality and experimental design can bias research findings and discuss how this methodology can be used to amalgamate stroke research.

157 words

2. Introduction:

Stroke is the third most prevalent cause of death in the developed world following cardiovascular disease and cancer [2]. It is a leading cause of serious and long-term disability in the United States[3] and the American Stroke Association estimate the cost at $62.7 billion for 2007[4]. Stroke has been researched for over 20 years and more than 1000 neuroprotective interventions have been investigated[1]. An understanding of the pathophysiology of stroke is crucial to the identification of steps to be targeted in the ischemic cascade. Here we use systematic review and meta-analysis to amalgamate the existing data and increase the value of the available evidence.

These techniques have been used to identify aspects of experimental protocol which appear to affect the accuracy of the outcome measures in stroke studies and describe their importance in the translation of efficacy from animal to human research. The CAMARADES group has generated significant evidence supporting the need to improve the procedures used in experimental stroke studies and encouraging the systematic evaluation of animal data before proceeding to clinical trials [5,6,7,8].

Glutamate, an excitatory amino acid (EAA), is the main excitatory transmitter in the central nervous system. It acts at four EAA receptor subtypes; NMDA, AMPA, kainate and metabotropic. The NMDA receptor is a G-protein coupled receptor with a calcium permeable channel that mediates slow excitatory transmission of action potentials. Excessive influx of calcium resulting from NMDA receptor activation can cause excitotoxic cell death. The discovery of EAA antagonists has improved our understanding of the pathophysiological role of glutamate however they have not been successfully developed for clinical use. Dizocilpine (MK801) is an NMDA receptor antagonist that blocks the calcium channel to prevent excitotoxic calcium influx.

The aim of this study was to use systematic review and meta-analysis to amalgamate stroke data using the effect of MK801 in models of stroke. We hope to generate evidence for the involvement of the NMDA receptor in stroke pathophysiology. Our analysis aims to identify any study characteristics that may affect the accuracy of the experimental findings or explain the difficulty in translating EAA antagonists from preclinical to clinical use.

3. Methods:

All methods were adapted from those developed by Macleod and colleagues described below [5].

Systematic Review: A comprehensive search of three electronic databases was used. Pubmed (1974 – March 2007), Embase (1980 – March 2007) and BIOSIS (1969 – March 2007). Search criteria: [((Glutamate) OR (GLU) OR (Glutamic Acid)) AND ((NMDA) OR (N-methyl-D-aspartic acid) OR (N methyl dextro aspartic acid) OR (N methyl dextro aspartate) OR (N methyl D aspartate)) AND ((Stroke) OR (Ischemia))].

Inclusion Criteria: The title and abstract of each reference was amalgamated into a reference manager. Duplicates were excluded and hard copies obtained, facilitating the systematic search which selected all studies reporting the effect of MK801 in a model of stroke. Uncertainty about the selection of studies was resolved in discussion with a second investigator.

Methods of Review: We aimed to describe all evidence for the involvement of the NMDA receptor in stroke by presenting the activity of MK801 in all experimental stroke approaches. To describe the range and quality of studies we extracted evidence from each paper according to a modified version of the STAIR criteria – recommendations made by the Stroke Academic Industry Roundtable[9]. Evidence was extracted to show that MK801:

(i) was tested in two or more laboratories,
(ii) two or more species,
(iii) animals with co-morbidities,
(iv) male and female animals,
(v) permanent and temporary models of ischemia,
(vi) at least 1 hour after vessel occlusion,
(vii) at least two doses,
(viii) via a route of delivery that is applicable to man,
(ix) reporting both histological and neurobehavioural outcomes,
(x) measured at least four weeks after vessel occlusion and
(xi) in a non-rodent species. [9]

To assess study quality each paper was scored against the CAMARADES eleven item checklist[5]:

(i) Peer reviewed publication,
(ii) statement of control of temperature,
(iii) statement of control of physiological variables,
(iv) randomised allocation to group,
(v) blinded induction of stroke model,
(vi) blinded assessment of outcome,
(vii) avoidance of anaesthetics with reported neuroprotective properties,
(viii) use of co-morbid animals,
(ix) sample size calculation,
(x) statement of compliance with regulations and
(xi) statement of potential conflict of interest.

Data Extraction:

The Pathophysiology of Stroke: To begin the process of research synthesis, a 'comparison' was described as 'the assessment of outcome in treatment and control groups following treatment with a given dose of MK801 or vehicle, with treatment at a given time before of after the induction of an in vivo or in vitro model of stroke'. Entries were grouped according to outcome measure:

- Lesion volume,
- Cellular survival assay,
- Neurological score or
- Other.

The 'other' group encompassed assessment of protein abundance, RNA abundance, chemical assay, physiological variables, cellular morphology and electrophysiology. Study quality was then evaluated.

Infarct Volume: In order to further assess the neuroprotective effect of MK801 in stroke, comparisons where infarct volume was reported after the induction of middle cerebral artery occlusion (MCAO) or excitotoxin exposure were examined. For each comparison number of animals in treatment and control groups, mean outcome and standard deviation (SD) were extracted. The total dose of MK801 administered in the first 24 hours following induction was recorded to allow the appropriate comparison of studies where multiple doses or continuous infusion were applied. In instances where numerical data were not reported, values were read off the graphs.

Meta-analysis: Using weighted mean difference analysis with a random effects model the effect size of each infarct volume comparison was combined to give a global estimate of efficacy. Division of the number of animals (n) in the control group by n of the treatment group allowed for adjustment of effect size where a single control group served multiple comparisons. These data were then normalised to the outcome in the control group as follows:

$$Effect(\%) = 100 * \left(\frac{Outcome[Control] - Outcome[Treated]}{Outcome[Control]} \right)$$

To assess the impact of study variables on the global estimate of efficacy the data were stratified according to: drug dose, dosing regime, time of administration, route of administration, reported quality score, outcome measure, time of outcome measurement, anaesthetic used, model of stroke, type of ischemia, use of co-morbid animals, sex and species of animal.

Partitioning heterogeneity and χ^2 distribution with n-1 degrees of freedom (df) were used to assess the significance of differences between n groups. The significance level of $p<0.001$ was used to allow for multiple comparisons.

4. Results:

Systematic Search: The initial search criteria of [((glutamate) OR (GLU) OR (glutamic acid)) AND ((stroke OR Ischemia))] produced > 14,000 articles. To refine the search we decided to focus on glutamate at the NMDA receptor which generated 3405 articles. Following removal of duplicates and those articles not fulfilling the inclusion criteria 1053 references remained.

During examination of the abstracts a number of drugs including MK801, quinolinate, riluzole, memantine and dextrorphan were regularly employed as research tools in stroke. We decided to begin the synthesis of this volume of research by focusing on MK801 finding a total of 316 relevant articles. 81% of these (a total of 257) were obtained in hard copy and evaluated according to the methodology. Following examination of each paper 381 experiments from 166 articles were entered into the database including 77 comparisons containing outcome measures of lesion volume.

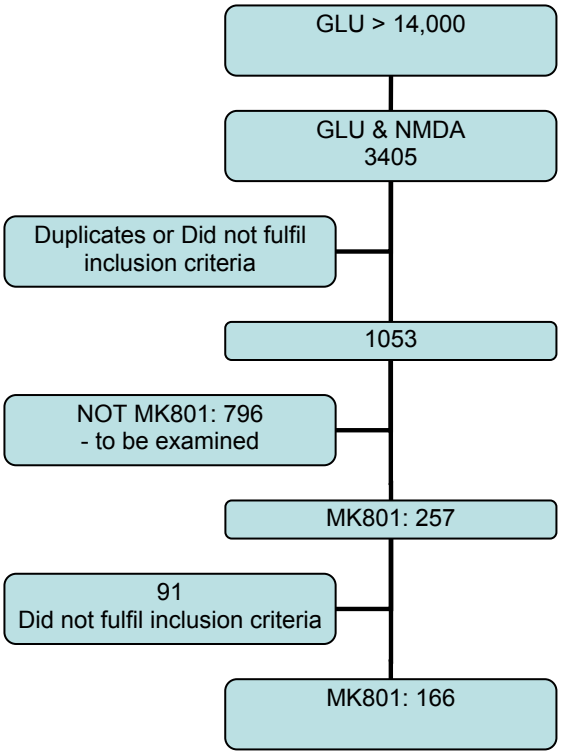

Fig1. Flow diagram of the systematic search

Systematic Review of MK801 in Stroke:

381 comparisons describing the effect of MK801 in a model of stroke were extracted and are described in Table 1 and Appendix 2. Of these comparisons; 211 were conducted in vivo, 54 in tissue slice and 116 in neuronal culture. Outcome measures varied greatly and were combined into four groups for evaluation. Of the 77 comparisons reporting lesion volume, 97% were conducted in vivo and 3% in neuronal culture. The mean quality score for these data was 4.5 out of 11. 102 comparisons reported a cellular survival assay, 63 of which detailed neuronal viability and 26 reporting LDH assay. These comparisons were conducted at all three levels and generated a mean quality score of 2.8. The 14 comparisons reporting neurological scores were conducted solely in vivo with a mean quality score of 2.9. The remaining 188 comparisons described research at all three levels and reported an extensive range of outcomes. The mean quality score for these data was 3.2.

		Outcome Measure			
	Total No Experiments	Lesion Volume	Cellular Survival Assay	Neurological Score	Other
n	381	77	102	14	188
Level of Study	Number of Comparisons at Each Level				
In vivo	211	75	32	14	90
Neuronal Culture	116	2	54		60
Tissue Slice	54		16		38
Mean Quality Score	3.4	4.5	2.8	2.9	3.2

Table 1: Study Characteristics Summary (see Appendix 2).

Quality Score Analysis:

The mean quality score for all existing research exploring the effect of MK801 in models of stroke is 3.4 of a possible 11. While 82% of methods controlled temperature, just 23% described the control of other physiological variables. 5% reported random allocation to experimental group and 1% blinded investigators at the induction of the stroke model. 18% reported blinded assessment of outcome. 3% of these investigations examined the effects of MK801 in co-morbid animals.

		Outcome Measure			
	Total No Experiments	Lesion Volume	Cellular Survival Assay	Neurological Score	Other
Quality Item	% Achieving Each Quality Criterion				
Peer Review Publication	100	100	100	100	100
Control of Temperature	82	94	81	36	82
Control of Physiological Variables	23	48	11	21	20
Random Allocation to Group	5	5	3	7	6
Blinded Induction of Stroke Model	1	4	0	7	1
Blinded Assessment of Outcome	18	40	16	14	11
Anaesthetic without intrinsic neuroprotective activity	55	86	38	71	49
Use of Co-morbid Animals	3	9	1	0	3
Sample Size Calculation	0	0	0	0	0
Compliance with Animal Welfare Regulations	39	45	31	36	41
Statement of Potential Conflicts of Interest	8	19	3	0	6

Table 2: Quality Scores Summary (see Appendix 3)

Meta-analysis of the Effect of MK801 on Infarct Volume:

The systematic search identified 35 original papers reporting lesion volume with and without MK801 treatment. We extracted 77 comparisons reporting lesion volume of which 45 used an MCAO model, 24 induced an excitotoxic lesion and 8 were excluded from the meta-analysis as they did not report sufficient experimental detail for data extraction [Appendix1,89]. This analysis is therefore based upon data from 34 full publications describing the effect of MK801 in 2 models of experimental stroke, published between 1988 and 2007 [Appendix1&2]. These 77 comparisons describe the effect of MK801 on infarct volume in 1098 animals.

MK801 in MCAO:

Study Range and Quality: Models of MK801 in MCAO included 26 comparisons of permanent ischemia, 9 of temporary ischemia and 8 of thrombotic ischemia induced by six different methods and involving 699 animals. The median reported quality score was 4 with a range from 2-6. The quality score assessment of study characteristics showed that no study performed a sample size calculation, just 2 comparisons describe random allocation to experimental group and 3 reported blinded induction of MCAO. Assessment of outcome was blinded in 17 comparisons and 6 comparisons reported the effect of the drug in animals with co-morbidities. Stratifying the data according to study quality showed that effect size of MK801 was significantly higher in studies with lower quality scores and declined as study quality improved (χ^2=59,df=44,p<0.001;Fig2a).

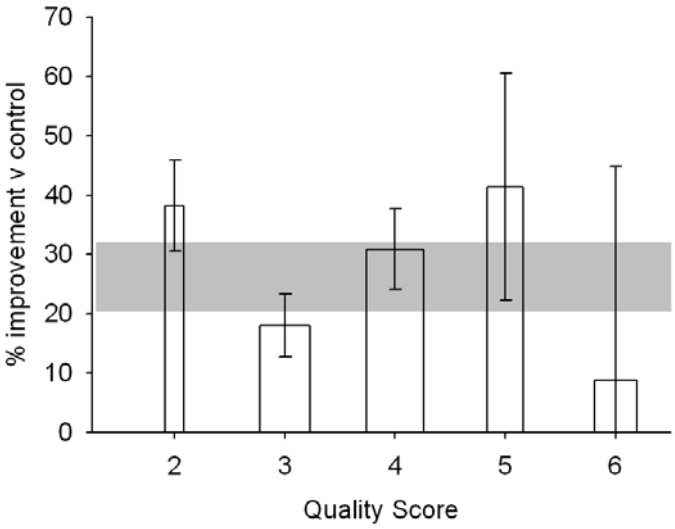

Fig2a: Effect of quality on estimate of efficacy of MK801 in MCAO.

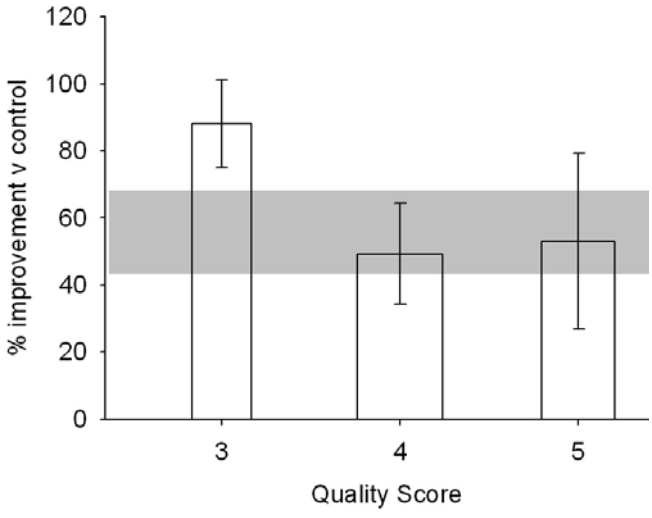

Fig2b: Effect of quality on estimate of efficacy of MK801 in Excitotoxin-induced lesions.

Effect Size: Overall MK801 was reported to reduce infarct volume by 26.3% (95% confidence limits 20.6%-32%,p<0.001) in MCAO models of stroke. The effect size was significantly higher in healthy than in hypertensive animals (χ^2=29,df=44,p<0.001;Fig 3a), in permanent ischemia than in temporary or thrombotic occlusion (χ^2=37,df=44,p<0.001;Fig 3b) and in cat models than the rat or mouse (χ^2=16,df=44,p<0.001;Fig 3c). Thiopental anaesthesia generated the highest effect size (50.6%) and infarct volume was significantly altered by the choice of anaesthetic (χ^2=69,df=44, p<0.001;Fig 3d). The method of MCAO induction (χ^2=41,df=44,p<0.001;Fig 4a) and route of administration of the drug (χ^2=37,df=44,p<0.001;Fig 4b) also significantly affected the reported effect size.

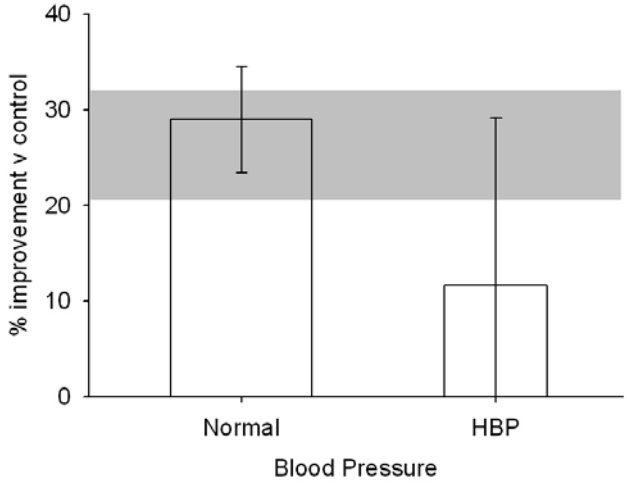

Fig3a:Effect of high blood pressure on estimate of efficacy of MK801 in MCAO.

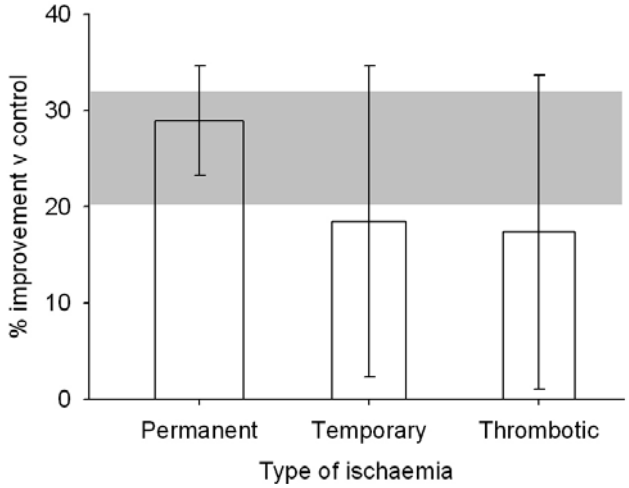

Fig3b:Effect of type of ischemia on estimate of efficacy of MK801 in MCAO.

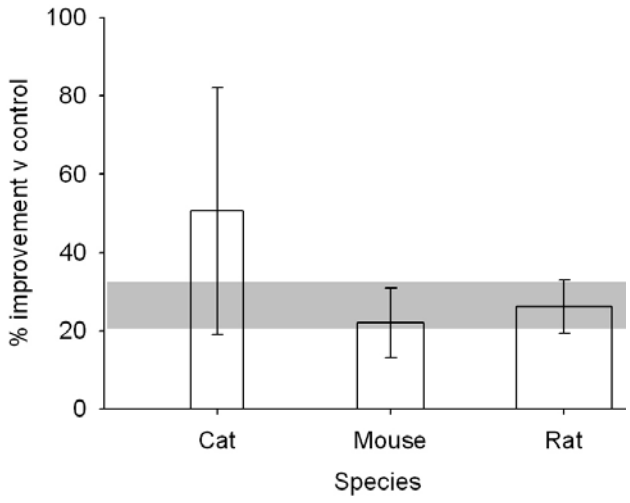

Fig3c:Effect of species on estimate of efficacy of MK801 in MCAO.

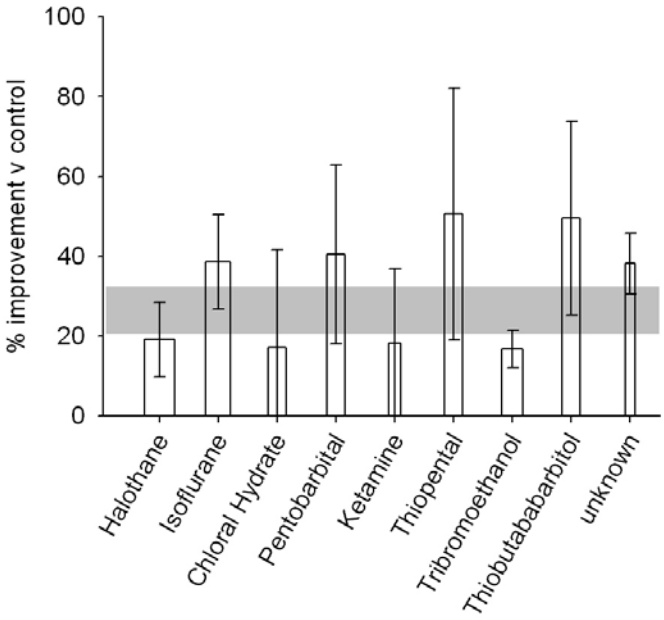

Fig3d:Effect of anaesthetic on estimate of efficacy of MK801 in MCAO.

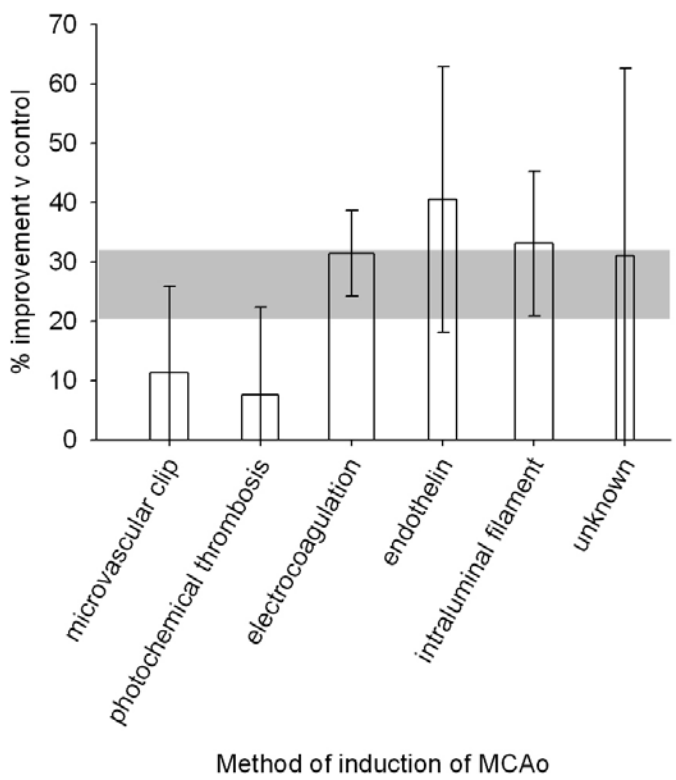

Fig4a: Effect of the method of induction of ischemia on estimate of efficacy of MK801 in MCAO.

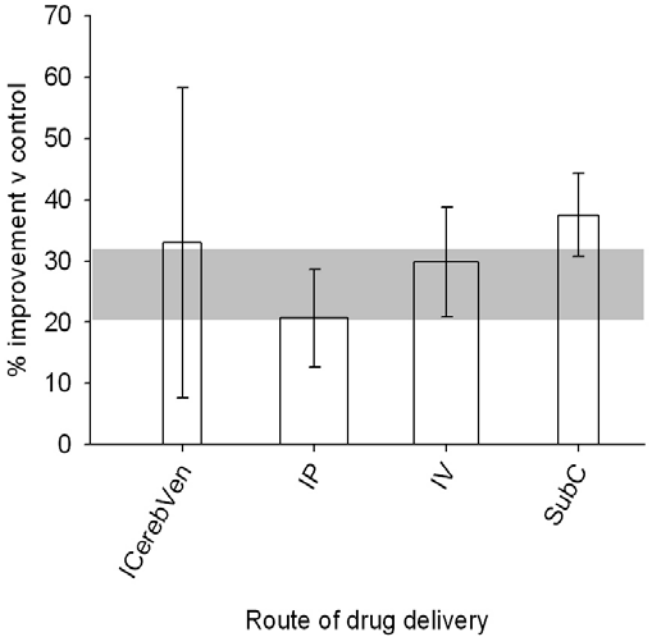

Fig4b: Effect of the route of drug delivery on estimate of efficacy of MK801 in MCAO.

MK801 in Excitotoxic Lesion:

Study Range and Quality: Models of MK801 in excitotoxin induced models of stroke included 21 comparisons following intrastriatal injection, 1 following microdialysis with glutamate and 2 following intraperitoneal (IP) injection of an excitotoxin. Median reported quality score was 4 with a range from 3-5. No studies used animals with co-morbidities, reported a sample size calculation or blinded investigators at induction of the model. 2 comparisons stated random allocation to experimental group and 10 blinded the assessment of outcome. Stratifying the data according to study quality showed that effect size was significantly higher in studies with lower quality scores (χ^2=25,df=23,p<0.001;Fig2b).

Effect Size: MK801 was reported to reduce excitotoxic lesion volume by 55.9% (95% confidence limits 43.6%-68.1%,p<0.001). Effect size of MK801 was significantly higher where animals were not randomly allocated to group (χ^2=21,df=23,p<0.001;Fig5a), where MK801 was delivered IP (χ^2=15,df=23,p<0.001;Fig5b) and in mouse models (χ^2=12,df=23,p<0.001;Fig5c). The method of induction of each lesion had a significant effect on the outcome (χ^2=27,df=23,p<0.001;Fig5d).

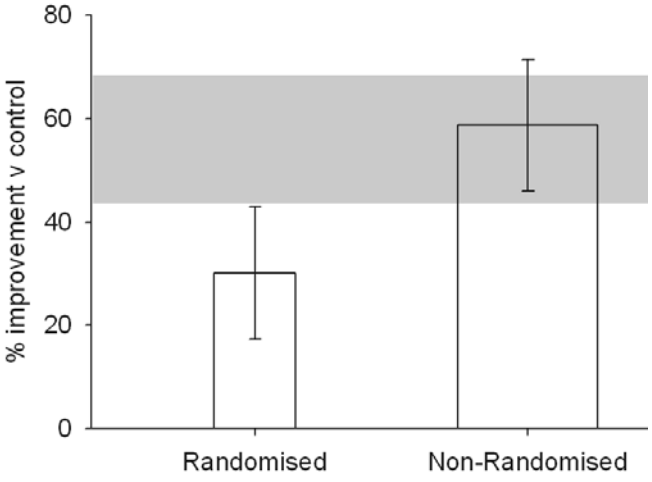

Fig5a:Effect of randomisation on estimate of efficacy of MK801 in Excitotoxicity.

Fig5b: Effect of the route of drug delivery on estimate of efficacy of MK801 in Excitotoxicity.

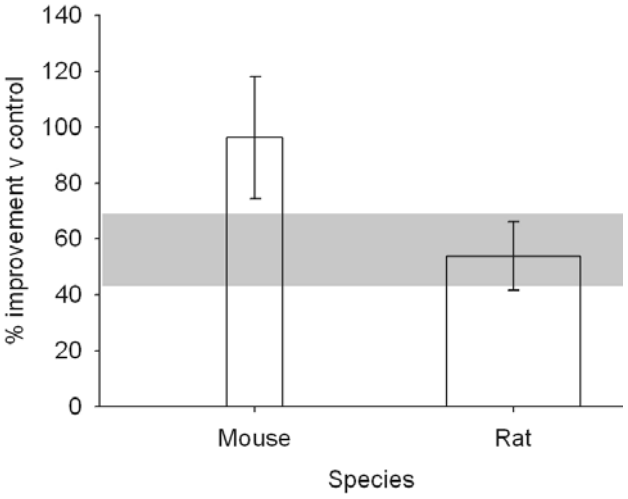

Fig5c:Effect of species on estimate of efficacy of MK801 in Excitotoxicity.

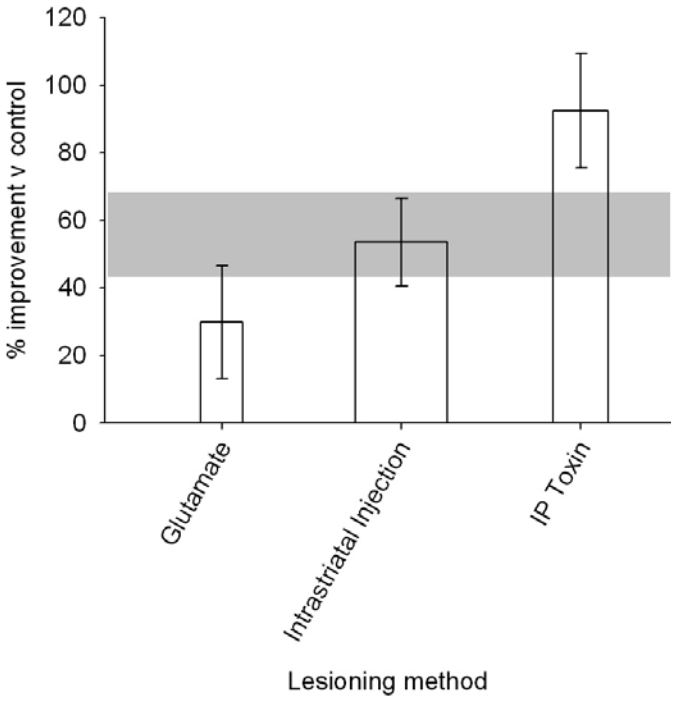

Fig5d:Effect of lesioning method on estimate of efficacy of MK801 in Excitotoxicity.

5. Discussion:

Systematic Review:

From the systematic review of currently available literature reporting the pathophysiology of stroke we have shown that there is a large volume of evidence and demonstrated a methodology to amalgamate these data. During the process of the review it has become clear that the best approach to reviewing this vast body of evidence is to ask specific questions and we have achieved this by focusing on one receptor at a time. Evaluating the evidence for the involvement of the NMDA receptor alone allowed us to examine in detail just one step in the ischemic cascade. Systematic review and meta-analysis could be used to assess all other NMDA antagonists and agonists to build an evidenced understanding of its significance in stroke. Continuing this process with other steps in the stroke cascade may enable us to refine our knowledge and understanding of stroke and to target our research and development choices.

Study Quality:

As previously demonstrated by the CAMARADES group, the assessment of experimental quality can identify where methodological characteristics may impact upon estimates of efficacy[7]. The overall quality score is low and in the MCAO and excitotoxin models quality bears a significant inverse relationship with the estimate of effect size. The difference between overall effect size in the MCAO and excitotoxic models may be real but we must consider the influence of the individual study characteristics on the reported outcome.

In MCAO studies MK801 had a significantly reduced effect size in hypertensive animals. However, these results must be interpreted with caution as only 3% of studies reported the use of co-morbid animals. This is further confounded as no co-morbid animals were used in the excitotoxic model and the effect size here may have been overestimated. Testing MK801 in hypertensive animals may have important implications for its clinical use due to the high prevalence of hypertension in stroke patients.

Random allocation of animals to treatment or control and blinding investigators during induction and assessment of outcome were poorly scored throughout the comparisons. These factors are considered important for the reduction of bias and are routine in clinical trials. In the excitotoxic lesion analysis where random allocation to group was reported the estimate of effect size was significantly reduced. No comparisons in this group blinded induction so the reported effect size of MK801 should be considered with care and may be overestimated due to bias.

In MCAO models effect size was significantly reduced when MK801 was delivered intraperitoneally (IP) while IP delivery significantly increased effect size in the excitotoxic model. IP was the most commonly employed route of delivery in MCAO and excitotoxic studies and was tested in the largest numbers of animals. This may be a true finding or may have resulted from an inappropriate comparison within the analysis but it warrants further exploration into the impact that route of drug delivery can have upon the effect size. It may be of importance in the translation of this efficacy into clinical trials.

Limitations of the Study:

There are systematic and objective limitations to the analysis. The search strategy and exclusion criteria allow a subjective element to influence selection of articles. I suggest that employing two independent reviewers would reduce bias. Where numerical data were unpublished values were read off graphs, introducing further bias to the study. It is preferable to request raw data from the authors but due to time limitations this was not achievable.

Comparing quality scores for in vivo and in vitro studies using the same CAMARADES criteria produces bias towards in vivo reports. Perhaps separate quality criteria for assessment of in vitro research would represent the experiments more appropriately. Nonetheless the importance of these quality criteria in the reduction of biological and systematic bias is clear and awareness of this relationship could increase the value and comparability of data generated in vivo and in vitro.

Publication bias is an important consideration. We aimed to amalgamate all evidence for the effect of MK801 in stroke but using full publications as the source introduces inherent bias. It has been shown that neutral studies are less likely to be published than those reporting positive findings[10] and if this is the case we may have substantially overestimated the effect size of the drug. It is also conceivable that our search strategy may not have identified all relevant articles.

It is important to note that performing a sub-group analysis in this way stratifies each criterion and may give rise to some inappropriate data comparisons. We must consider that chance, bias and confounding factors may contribute to the findings. For example in the excitotoxic lesion analysis effect size is significantly higher in mice than in rats. However MK801 was only applied to mice in 1 comparison reporting its effect in 12 animals. 23 comparisons treating 387 rats reported a significantly lower effect size of MK801. This is an inappropriate data comparison and the trend should be interpreted with caution.

Suggestions for Further Research:

To realise the full value of this evidence we should first continue the evaluation of the effect of MK801 using stratified meta-analysis for the most commonly used outcome measures; neuronal viability, LDH assay and calcium assay. Continuing the analysis using other NMDA antagonists and then agonists of the receptor will allow us to state with confidence whether NMDA blockade is in fact neuroprotective in stroke. Using these methods to evaluate the evidence for the involvement of other receptors in the stroke cascade will allow us to generate a well evidenced pathway for the pathophysiology of stroke which we hope can be used to select targets for further stroke research and drug development.

6. Conclusions:

Systematic review of the current research evaluating MK801 in stroke has shown that study quality and the value of evidence could be improved. MK801 improves outcome by 26.3% and 55.9% respectively in MCAO and excitotoxic models of stroke where outcome is measured as lesion volume. The estimation of effect size using other outcome measures for MK801 and furthering this process for other NMDA antagonists and agonists would produce an estimate of overall importance of NMDA in the stroke pathway. This method could be applied to other stages of the stroke cascade allowing the synthesis of the existing research in stroke to describe stroke pathophysiology.

2983 words

7. Acknowledgements:

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Appendix 1:

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Appendix 2: *Study Characteristics Report*

Author	*Year*	*Drug*	*Species*	*Total No. Animals*	*Dose Range*	*Time of Admin (mins)*	*Anaesthetic*	*Type of Ischaemia*	*Route of Delivery*	*Outcome Measure(s)*	*Level of Study*
Almaas,R (1)	2002	MK801	Human		10uM	0-			Unknown	Cellular Survival Assay	neuronal culture
Almaas,R (1)	2002	MK801	Human		10uM	0-			Unknown	Other	neuronal culture
Anderson,T (2)	2002	MK801	Rat		100uM	-15	Unknown			Other	Tissue Slice
Andras,I (3)	2007	MK801	Rat		10uM	-15				Other	neuronal culture
Aono,M (4)	2002	MK801	Rat		10uM	-30				Cellular Survival Assay	neuronal culture
Aono,M (4)	2002	MK801	Rat		10uM	-30				Other	neuronal culture
Arias,R (5)	1999	MK801	Rat		0.01-1uM	0	Ketamine			Cellular Survival Assay	Tissue Slice
Armstead,W (6)	2002	MK801	Pig		10uM	-30	Isoflurane	Temporary		Other	In vivo
Ault,B (7)	1995	MK801	Mouse		-	-				Other	neuronal Culture
Back,T (8)	2000	MK801	Rat	19	3mg/kg	10-	Halothane	Permanent	SubC	Cellular Survival Assay	In vivo
Back,T (8)	2000	MK801	Rat	19	3mg/kg	10-	Halothane	Permanent	SubC	Lesion Volume	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Back,T (8)	2000	MK801	Rat	19	3mg/kg	10-	Halothane	Permanent	SubC	Other	In vivo
Bakker,M (9)	1991	MK801	Rat		-	-	Equithesin			Other	In vivo
Beck,J (10)	2003	MK801	Rat		-	-	Halothane			Cellular Survival Assay	neuronal culture
Berger,C (11)	2004	MK801	Rat	12	1mg/kg	30-	Ketamine	Permanent	IV	Other	In vivo
Berger,C (11)	2004	MK801	Rat	12	1mg/kg	30-	Ketamine	Permanent	IV	Lesion Volume	In vivo
Bernabeu,R (12)	2000	MK801	Gerbil		-	-	Isoflurane	Temporary		Cellular Survival Assay	In vivo
Bickler,P (13)	1994	MK801	Rat		-	-	Enflurane	Temporary		Cellular Survival Assay	Tissue Slice
Bickler,P (13)	1994	MK801	Rat		-	-	Enflurane	Temporary		Other	Tissue Slice
Black,M (14)	1992	MK801	Rat	12	4mg/kg	-30	Pentobarbital	Not Known	IP	Lesion Volume	In vivo
Bonde,C (15)	2005	MK801	Rat		-	-		Temporary		Cellular Survival Assay	Tissue Slice
Bonde,C (15)	2005	MK801	Rat		-	-		Temporary		Other	Tissue Slice

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Bruno,V (16)	1994	MK801	Mouse		-	-		Temporary		Cellular Survival Assay	neuronal culture
Bruno,V (16)	1994	MK801	Mouse		-	-		Temporary		Other	neuronal culture
Buchkremer-Ratzmann,I (17)	1997	MK801	Rat	29	0.5mg/kg	-30-	Halothane	Thrombotic	IV	Lesion Volume	In vivo
Buchkremer-Ratzmann,I (17)	1997	MK801	Rat	29	0.5mg/kg	-30-	Halothane	Thrombotic	IV	Other	In vivo
Burtrum,D (18)	1994	MK801	Rat		1mg/kg	-15-	ether			Other	In vivo
Burtrum,D (18)	1994	MK801	Rat		1mg/kg	-15-	ether			Lesion Volume	In vivo
Butcher,S (19)	1997	MK801	Rat	96	0.3-3mg/kg	1-	Pentobarbital		IV	Lesion Volume	In vivo
Butcher,S (19)	1997	MK801	Rat	96	0.3-3mg/kg	1-	Pentobarbital		IV	Other	In vivo
Butcher,S (19)	1997	MK801	Rat	32	0.3-5mg/kg	-30-	Pentobarbital	Thrombotic	IP	Other	In vivo
Butcher,S (19)	1997	MK801	Rat	32	0.3-5mg/kg	-30-	Pentobarbital	Thrombotic	IP	Lesion Volume	In vivo
Campos-Gonzalez,R (20)	1992	MK801	Gerbil		-	-	Pentobarbital	Temporary		Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Cardenas,A (21)	2000	MK801	Rat		-	-		Temporary		Cellular Survival Assay	Tissue Slice
Cardenas,A (21)	2000	MK801	Rat		-	-		Temporary		Other	Tissue Slice
Carter,C (22)	1988	MK801	Rat		-	-	Halothane			Other	Tissue Slice
Cavallini,S (23)	2005	MK801	Rat		-	-	ether			Other	Tissue Slice
Cho,S (24)	2004	MK801	Rat		-	-				Cellular Survival Assay	Tissue Slice
Collaco-Moraes,Y (25)	1993	MK801	Rat		3mg/kg	-5	Pentobarbital	Permanent		Other	In vivo
Comelli,M (26)	1993	MK801	Rat	19	1mg/kg	-60-	Halothane	Thrombotic	IV	Lesion Volume	In vivo
Comelli,M (26)	1993	MK801	Rat	19	1mg/kg	-60-	Halothane	Thrombotic	IV	Other	In vivo
Comelli,M (27)	1992	MK801	Rat		1mg/kg	-60	Halothane	Thrombotic		Other	In vivo
Connell,B (28)	2007	MK801	Rat	33	0.005-0.5mg/kg	-75-	thiobutababarbitol	Permanent	IV	Other	In vivo
Connell,B (28)	2007	MK801	Rat	33	0.005-0.5mg/kg	-75-	thiobutababarbitol	Permanent	IV	Lesion Volume	In vivo
Connell,B (28)	2007	MK801	Rat		-	-	Isoflurane			Other	Tissue Slice

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Dalkara,T (29)	1990	MK801	Rat		-	-	Urethane	Temporary		Other	In vivo
Danilczuk,Z (30)	2006	MK801	Mouse		-	-	Pentobarbital			Neurological Score	In vivo
Danilczuk,Z (30)	2006	MK801	Mouse		-	-	Pentobarbital			Other	In vivo
Danilczuk,Z (31)	2005	MK801	Mouse		-	-				Cellular Survival Assay	In vivo
Danilczuk,Z (31)	2005	MK801	Mouse		-	-				Neurological Score	In vivo
Danilczuk,Z (31)	2005	MK801	Mouse		-	-				Other	In vivo
Dawson,V (32)	1996	MK801	Mouse		-	-				Other	neuronal culture
Dawson,V (32)	1996	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Dean,J (33)	2006	MK801	Sheep		-	-	Halothane			Other	In vivo
Dean,J (33)	2006	MK801	Sheep		-	-	Halothane			Cellular Survival Assay	In vivo
Djali,S (34)	2001	MK801	Rat		-	-				Other	Tissue Slice

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Djuricic,B (35)	1994	MK801	Rat		-	-	Halothane			Other	Tissue Slice
Duhaime,A (36)	1990	MK801	Rat		-	-	Chloral Hydrate			Cellular Survival Assay	In vivo
Duhaime,A (36)	1990	MK801	Rat		-	-	Chloral Hydrate			Other	In vivo
Endres,M (37)	1998	MK801	Mouse	24	3mg/kg	-10-	Halothane	Temporary	IP	Neurological Score	In vivo
Endres,M (37)	1998	MK801	Mouse	24	3mg/kg	-10-	Halothane	Temporary	IP	Lesion Volume	In vivo
Endres,M (37)	1998	MK801	Mouse	24	3mg/kg	-10-	Halothane	Temporary	IP	Other	In vivo
Engidawork,E (38)	2001	MK801	Rat		-	-				Other	In vivo
Esquenazi,S (39)	2002	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Esquenazi,S (39)	2002	MK801	Mouse		-	-				Other	neuronal culture
Farfel,G (40)	1995	MK801	Rat		-	-	Pentobarbital			Other	In vivo
Felt,B (41)	2002	MK801	Rat		-	-	Isoflurane			Neurological Score	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Felt,B (41)	2002	MK801	Rat		-	-	Isoflurane			Neurological Score	In vivo
Foster,A (42)	1993	MK801	Rat		-	-	Equithesin			Other	In vivo
Franceschini,D (43)	2006	MK801	Rat		-	-				Other	neuronal culture
Franceschini,D (43)	2006	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Fujiki,M (44)	2004	MK801	Gerbil		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo
Fujisawa,H (45)	1993	MK801	Rat	15	0.5mg/kg	-30-	Halothane	Temporary	IV	Lesion Volume	In vivo
Fujisawa,H (45)	1993	MK801	Rat	15	0.5mg/kg	-30-	Halothane	Temporary	IV	Other	In vivo
Garcia,J (46)	2003	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Garcia,J (46)	2003	MK801	Rat		-	-				Other	neuronal culture
Garcia,J (47)	2001	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Ge,Q (48)	2006	MK801	Rat		-	-		Temporary		Cellular Survival Assay	neuronal culture

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Ge,Q (48)	2006	MK801	Rat		-	-		Temporary		Other	neuronal culture
Giffard,R (49)	1992	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Giffard,R (49)	1992	MK801	Mouse		-	-				Other	neuronal culture
Giffard,R (49)	1992	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Giffard,R (49)	1992	MK801	Mouse		-	-				Other	neuronal culture
Gill,R (50)	1991	MK801	Rat	60	0.184-1.84mg/kg	0	Isoflurane	Permanent	IV	Lesion Volume	In vivo
Gill,R (51)	1992	MK801	Rat	32	3mg/kg	30	Halothane	Permanent	IP	Lesion Volume	In vivo
Gilland,E (52)	1998	MK801	Rat		-	-	Halothane			Cellular Survival Assay	In vivo
Gilland,E (52)	1998	MK801	Rat		-	-	Halothane			Other	In vivo
Giovannelli,L (53)	2002	MK801	Rat	8	1mg/kg	-10-	Isoflurane	Permanent	SubC	Lesion Volume	In vivo
Giovannelli,L (53)	2002	MK801	Rat	8	1mg/kg	-10-	Isoflurane	Permanent	SubC	Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Greene,J (54)	1995	MK801	Rat	117	10mg/kg	-30	Chloral Hydrate	Not Known	IP	Lesion Volume	In vivo
Grojean,S (55)	2003	MK801	Rat		-	-				Cellular Survival Assay	In vivo
Grojean,S (55)	2003	MK801	Rat		-	-				Other	In vivo
Haraldseth,O (56)	1990	MK801	Rat		-	-	Halothane	Temporary		Other	In vivo
Hayward,N (57)	1993	MK801	Gerbil		-	-	Isoflurane	Temporary		Cellular Survival Assay	In vivo
Hernandez-Fonseca,K (58)	2005	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Herz,R (59)	1998	MK801	Rat	12	0.5mg/kg	30	Isoflurane		IV	Lesion Volume	In vivo
Herz,R (59)	1998	MK801	Rat	14	0.5mg/kg	30	Isoflurane	Permanent	IV	Lesion Volume	In vivo
Hewett,S (60)	1996	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Hewett,S (60)	1996	MK801	Mouse		-	-				Other	neuronal culture
Hewitt,K (61)	1991	MK801	Gerbil		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaestheti	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Himori,N (62)	1991	MK801	Mouse		-	-	Pentobarbital			Cellular Survival Assay	In vivo
Himori,N (62)	1991	MK801	Mouse		-	-	Pentobarbital	Temporary		Cellular Survival Assay	In vivo
Himori,N (62)	1991	MK801	Mouse		-	-	Pentobarbital			Neurological Score	In vivo
Himori,N (62)	1991	MK801	Mouse		-	-	Pentobarbital	Temporary		Neurological Score	In vivo
Hoffman,C (63)	1995	MK801	Gerbil		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo
Huang,Q (64)	1994	MK801	Rat		-	-	Pentobarbital			Other	In vivo
Ikonomidou,C (65)	1989	MK801	Rat		-	-	Halothane	Permanent		Lesion Volume	In vivo
Ikonomidou,C (65)	1989	MK801	Rat		-	-	Halothane	Permanent		Cellular Survival Assay	In vivo
Ishimaru,H (66)	1997	MK801	Gerbil		-	-	Halothane	Temporary		Other	In vivo
Ishimaru,H (66)	1997	MK801	Gerbil		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo
Jacobs,O (67)	1994	MK801	Rat		-	-	Chloral Hydrate			Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Kamiya,T (68)	2005	MK801	Rat		5mg/kg	-30-	Halothane	Permanent	IP	Other	In vivo
Kamiya,T (68)	2005	MK801	Rat		5mg/kg	-30-	Halothane	Permanent	IP	Lesion Volume	In vivo
Katchman,A (69)	1997	MK801	Rat		-	-				Other	Tissue Slice
Keana,J (70)	1989	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Kim,G (71)	2000	MK801	Mouse	12	10mg/kg	-15-	Chloral Hydrate	Not Known	IP	Other	In vivo
Kim,G (71)	2000	MK801	Mouse	12	10mg/kg	-15-	Chloral Hydrate	Not Known	IP	Lesion Volume	In vivo
Kim,W (72)	1999	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Kim,W (72)	1999	MK801	Rat		-	-				Other	neuronal culture
Kimura,M (73)	1998	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Kimura,M (73)	1998	MK801	Rat		-	-				Other	neuronal culture
Kinouchi,H (74)	1994	MK801	Rat		-	-	Halothane	Permanent		Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaestheti	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Kohmura,E (75)	1990	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Kolko,M (76)	2002	MK801	Rat		-	-				Other	neuronal culture
Kolko,M (76)	2002	MK801	Rat		-	-				Lesion Volume	neuronal culture
Kolko,M (76)	2002	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Kolko,M (76)	2002	MK801	Rat	17	5mg/kg	-5		Not Known	IP	Lesion Volume	In vivo
Kubo,T (77)	2001	MK801	Rat		-	-				Other	Tissue Slice
Kudo,M (78)	2001	MK801	Rat		-	-	Halothane			Cellular Survival Assay	neuronal culture
Kudo,M (78)	2001	MK801	Rat		-	-	Halothane			Other	neuronal culture
Kunimatsu,T (79)	2001	MK801	Rat		-	-	Urethane			Other	In vivo
Kwon,Y (80)	2000	MK801	Gerbil		-	-	Isoflurane	Temporary		Cellular Survival Assay	In vivo
Kwon,Y (80)	2000	MK801	Gerbil		-	-	Isoflurane	Temporary		Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Laake,J (81)	1999	MK801	Rat		-	-				Cellular Survival Assay	Tissue Slice
Lee,Y (82)	2004	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Lee,Y (82)	2004	MK801	Rat		-	-				Lesion Volume	neuronal culture
Lees,G (83)	1995	MK801	Rat		-	-	Halothane			Cellular Survival Assay	In vivo
Lehmann,A (84)	1992	MK801	Mouse		-	-	ether			Cellular Survival Assay	In vivo
Liniger,R (85)	2001	MK801	Rat		-	-	Halothane	Temporary		Cellular Survival Assay	Tissue Slice
Lippert,K (86)	1994	MK801	Rat		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo
Lippert,K (86)	1994	MK801	Mouse	40	1mg/kg	-60	Tribromoethanol	Permanent	IP	Lesion Volume	In vivo
Lippert,K (86)	1994	MK801	Rat		-	-		Not Known		Cellular Survival Assay	neuronal culture
Lobner,D (87)	1990	MK801	Rat		-	-				Other	Tissue Slice
Lobner,D (88)	1993	MK801	Rat		-	-		Temporary		Other	Tissue Slice

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Loscher,W (89)	1998	MK801	Rat		0.4mg/kg	-	Halothane	Permanent	IP	Neurological Score	In vivo
Luque,J (90)	2001	MK801	Rat	7	0.1mg/kg	-30-		Permanent	SubC	Other	In vivo
Luque,J (90)	2001	MK801	Rat	7	0.1mg/kg	-30-		Permanent	SubC	Lesion Volume	In vivo
Lustig,H (91)	1992	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Lustig,H (91)	1992	MK801	Rat		-	-				Other	neuronal culture
Lysko,P (92)	1992	MK801	Gerbil		-	-	Isoflurane	Temporary		Neurological Score	In vivo
Lysko,P (92)	1992	MK801	Gerbil		-	-	Isoflurane	Temporary		Cellular Survival Assay	In vivo
Lysko,P (92)	1992	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Ma,X (93)	2002	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Ma,X (93)	2002	MK801	Rat		-	-				Other	neuronal culture

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Mabuchi,T (94)	2001	MK801	Gerbil		-	-	Halothane			Cellular Survival Assay	In vivo
Mabuchi,T (94)	2001	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Margaill,I (95)	1996	MK801	Rat	34	1mg/kg	-5-30	Chloral Hydrate	Temporary	IV	Lesion Volume	In vivo
Marino,S (96)	2007	MK801	Rat		-	-				Other	neuronal culture
Massieu,L (97)	2000	MK801	Rat	22	1mg/kg	4410-	Halothane		IP	Other	In vivo
Massieu,L (97)	2000	MK801	Rat	22	1mg/kg	4410-	Halothane		IP	Lesion Volume	In vivo
Matsumoto,M (98)	1992	MK801	Rabbit		-	-	Halothane			Other	In vivo
Matsumoto,Y (99)	2004	MK801	Rat		-	-	ether			Cellular Survival Assay	neuronal culture
Matsumoto,Y (99)	2004	MK801	Rat		-	-	ether			Other	neuronal culture
Maus,M (100)	1999	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Maus,M (100)	1999	MK801	Mouse		-	-				Other	neuronal culture

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
McDonald,J (101)	1989	MK801	Rat		-	-	ether			Cellular Survival Assay	In vivo
Meloni,B (102)	2002	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Milusheva,E (103)	2003	MK801	Rat		-	-	ether			Other	Tissue Slice
Monnerie,H (104)	2003	MK801	Mouse		-	-				Other	neuronal culture
Monnerie,H (104)	2003	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Morioka,M (105)	1995	MK801	Rat		-	-				Other	neuronal culture
Moudy,A (106)	1994	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Moudy,A (106)	1994	MK801	Rat		-	-				Other	neuronal culture
Muir,J (107)	1996	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Muir,J (107)	1996	MK801	Mouse		-	-				Other	neuronal culture
Muir,J (107)	1996	MK801	Mouse		-	-				Other	neuronal culture

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Muir,J (107)	1996	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Nellgard,B (108)	1992	MK801	Rat		-	-	Isoflurane	Temporary		Cellular Survival Assay	In vivo
Nellgard,B (109)	1991	MK801	Rat		-	-	Isoflurane	Temporary		Cellular Survival Assay	In vivo
Newell,D (110)	1995	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Newell,D (111)	1995	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Newell,D (112)	1990	MK801	Unknown		-	-				Other	neuronal culture
Obrenovitch,T (113)	1997	MK801	Rat		-	-	Halothane			Other	In vivo
Oliveira,I (114)	2002	MK801	Rat		-	-				Cellular Survival Assay	Tissue Slice
Oliveira,I (114)	2002	MK801	Rat		-	-				Other	Tissue Slice
Olney,J (115)	1989	MK801	Rat		-	-	Halothane			Cellular Survival Assay	In vivo
Ozben,T (116)	2005	MK801	Rat		-	-	Urethane	Permanent		Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Ozyurt,E (117)	1988	MK801	Cat	18	5mg/kg	-30-	Thiopental	Permanent	IV	Lesion Volume	In vivo
Ozyurt,E (117)	1988	MK801	Cat	18	5mg/kg	-30-	Thiopental	Permanent	IV	Other	In vivo
Pang,Z (118)	2003	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Pang,Z (119)	1997	MK801	Rat		-	-				Other	neuronal culture
Pang,Z (119)	1997	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Paquet-Durand,F (120)	2004	MK801	Human		-	-				Cellular Survival Assay	neuronal culture
Paquet-Durand,F (120)	2004	MK801	Human		-	-				Other	neuronal culture
Park,C (121)	1989	MK801	Rat		-	-	Halothane			Other	In vivo
Park,C (122)	1988	MK801	Rat	20	0.5mg/kg	-30-30	Halothane	Permanent	IV	Lesion Volume	In vivo
Park,C (123)	1988	MK801	Cat	15	5mg/kg	120	Thiopental	Permanent	IV	Lesion Volume	In vivo
Pauwels,P (124)	1989	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Pearlstein,R (125)	1998	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Pocock,J (126)	1998	MK801	Rat		-	-				Other	neuronal culture
Prehn,J (127)	1993	MK801	Mouse	22	1mg/kg	-60	Tribromoethanol	Permanent	IP	Lesion Volume	In vivo
Pringle,A (128)	1997	MK801	Rat		-	-				Cellular Survival Assay	Tissue Slice
Pulsinelli,W (129)	1993	MK801	Rat	47	10mg/kg	-30-	Halothane	Permanent	IP	Lesion Volume	In vivo
Pulsinelli,W (129)	1993	MK801	Rat	47	10mg/kg	-30-	Halothane	Permanent	IP	Other	In vivo
Pulsinelli,W (129)	1993	MK801	Rat	47	10mg/kg	-30-	Halothane	Permanent	IP	Cellular Survival Assay	In vivo
Regan,R (130)	1996	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture
Remblier,C (131)	1999	MK801	Rat		-	-	Pentobarbital			Other	In vivo
Robert,F (132)	2002	MK801	Rat		-	-				Other	Tissue Slice
Robertson,S (133)	1997	MK801	Dog		-	-	Halothane			Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Rogers,B (134)	1989	MK801	Rat		-	-	Metophane			Neurological Score	In vivo
Rudolph,J (135)	1997	MK801	Unknown		-	-				Cellular Survival Assay	neuronal culture
Saez-Valero,J (136)	2003	MK801	Rat		-	-		Temporary		Other	Tissue Slice
Sarraf-Yazdi,S (137)	1998	MK801	Rat	36	1mg/kg	-30-	Isoflurane	Temporary	IP	Lesion Volume	In vivo
Sarraf-Yazdi,S (137)	1998	MK801	Rat	36	1mg/kg	-30-	Isoflurane	Temporary	IP	Neurological Score	In vivo
Schulz,J (138)	1995	MK801	Rat	56	5mg/kg	-60-	Pentobarbital		IP	Cellular Survival Assay	In vivo
Schulz,J (138)	1995	MK801	Rat	56	5mg/kg	-60-	Pentobarbital		IP	Lesion Volume	In vivo
Schurr,A (139)	1995	MK801	Rat		-	-				Other	Tissue Slice
Serteser,M (140)	2002	MK801	Rat		-	-	Urethane	Permanent		Other	In vivo
Sheardown,M (141)	1993	MK801	Gerbil		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo
Shirotani,T (142)	1994	MK801	Rat		-	-	Halothane	Permanent		Other	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Speliotes,E (143)	1994	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Stevens,M (144)	1990	MK801	Cat		-	-	Halothane	Temporary		Other	In vivo
Strasser,U (145)	1995	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Streit,W (146)	1992	MK801	Rat		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo
Sturm,C (147)	1993	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Sullivan,B (148)	2002	MK801	Rat		-	-	Halothane			Cellular Survival Assay	Tissue Slice
Thatcher,N (149)	1999	MK801	Guinea		-	-				Other	Tissue Slice
Veldhuis,W (150)	2003	MK801	Rat	52	1mg/kg	-15	ether		IP	Lesion Volume	In vivo
Velly,L (151)	2003	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Velly,L (151)	2003	MK801	Rat		-	-				Other	neuronal culture
Volbracht,C (152)	2006	MK801	Mouse		-	-				Cellular Survival Assay	neuronal culture

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Vornov,J (153)	1995	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Wahlestedt,C (154)	1993	MK801	Rat	10	1mg/kg	30	Halothane		IV	Lesion Volume	In vivo
Weaver,C (155)	1998	MK801	Rat		-	-				Cellular Survival Assay	neuronal culture
Weaver,C (155)	1998	MK801	Rat		-	-				Other	neuronal culture
Wenk,G (156)	1995	MK801	Rat		-	-	Pentobarbital			Neurological Score	In vivo
Whishaw,I (157)		MK801	Rat		-	-				Other	Tissue Slice
Whittingham,T (158)	1992	MK801	Gerbil		-	-				Other	Tissue Slice
Whittingham,T (158)	1992	MK801	Gerbil		-	-				Cellular Survival Assay	Tissue Slice
Xue,D (159)	1994	MK801	Rat	47	3mg/kg	90	Halothane	Temporary	IP	Lesion Volume	In vivo
Yamada,K (160)	1997	MK801	Rat	8	0.168mg	1440-	Halothane	Temporary	ICerebVen	Other	In vivo
Yamada,K (160)	1997	MK801	Rat	8	0.168mg	1440-	Halothane	Temporary	ICerebVen	Cellular Survival Assay	In vivo

Author	Year	Drug	Species	Total No. of Animals	Dose Range	Time of Admin (mins)	Anaesthetic	Type of Ischaemia	Route of Delivery	Outcome Measure(s)	Level of Study
Yamada,K (160)	1997	MK801	Rat	8	0.168mg	1440-	Halothane	Temporary	ICerebVen	Lesion Volume	In vivo
Yamada,Y (161)	1994	MK801	Rat		-	-				Other	neuronal culture
Yamashita,K (162)	1996	MK801	Rat	48	3mg/kg	3-	Halothane	Permanent	IP	Other	In vivo
Yamashita,K (162)	1996	MK801	Rat	48	3mg/kg	3-	Halothane	Permanent	IP	Lesion Volume	In vivo
Yao,H (163)	1994	MK801	Rat	10	1mg/kg	-30-	Halothane	Thrombotic	IP	Lesion Volume	In vivo
Yao,H (163)	1994	MK801	Rat	10	1mg/kg	-30-	Halothane	Thrombotic	IP	Other	In vivo
Yao,H (164)	1993	MK801	Rat	43	1mg/kg	-30	Halothane	Thrombotic	IP	Lesion Volume	In vivo
Yoneda,Y (165)	1993	MK801	Gerbil		-	-	ether	Temporary		Other	In vivo
Zhang,L (166)	1997	MK801	Gerbil		-	-	Halothane	Temporary		Cellular Survival Assay	In vivo

Appendix 3: *Study Quality Score Report*

Author	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*Quality Score*
Almaas,R	2002	+	+	+								+	4
Anderson,T	2002	+	+	+							+	+	5
Andras,I	2007	+											1
Aono,M	2002	+	+								+		3
Arias,R	1999	+						+					2
Armstead,W	2002	+	+					+			+		4
Ault,B	1995	+	+										2
Back,T	2000	+	+	+				+			+		5
Bakker,M	1991	+						+					2
Beck,J	2003	+	+					+					3
Berger,C	2004	+	+	+	+						+		5
Bernabeu,R	2000	+	+								+		3
Bickler,P	1994	+	+					+					3
Black,M	1992	+						+				+	3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Bonde,C	2005	+	+								+		3
Bruno,V	1994	+	+										2
Buchkremer-Ratzmann,I	1997	+	+					+			+		4
Burtrum,D	1994	+	+					+					3
Butcher,S	1997	+	+				+	+				+	5
Campos-Gonzalez,R	1992	+	+					+					3
Cardenas,A	2000	+	+								+		3
Carter,C	1988	+	+					+					3
Cavallini,S	2005	+	+				+	+			+		5
Cho,S	2004	+	+				+						3
Collaco-Moraes,Y	1993	+	+	+				+					4
Comelli,M	1992	+	+					+			+		4
Comelli,M	1993	+	+					+					3
Connell,B	2007	+	+	+				+			+		5

Author	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*Quality Score*
Dalkara,T	1990	+	+					+					3
Danilczuk,Z	2005	+									+		2
Danilczuk,Z	2006	+	+								+		3
Dawson,V	1996	+	+				+					+	4
Dean,J	2006	+	+		+		+	+			+		6
Djali,S	2001	+	+										2
Djuricic,B	1994	+						+			+		3
Duhaime,A	1990	+	+	+				+					4
Endres,M	1998	+	+	+		+		+					5
Engidawork,E	2001	+	+										2
Esquenazi,S	2002	+	+										2
Farfel,G	1995	+	+					+					3
Felt,B	2002	+						+					2
Foster,A	1993	+						+					2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Franceschini,D	2006	+									+		2
Fujiki,M	2004	+						+			+		3
Fujisawa,H	1993	+	+	+	+			+			+		6
Garcia,J	2001	+	+								+		3
Garcia,J	2003	+	+								+		3
Ge,Q	2006	+	+										2
Giffard,R	1992	+	+										2
Gill,R	1991	+	+	+			+	+					5
Gill,R	1992	+	+	+			+	+					5
Gilland,E	1998	+	+	+	+			+					5
Giovannelli,L	2002	+	+					+			+		4
Greene,J	1995	+	+					+			+		4
Grojean,S	2003	+	+								+		3
Haraldseth,O	1990	+	+	+				+					4

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Hayward,N	1993	+	+				+	+					4
Hernandez-Fonseca,K	2005	+									+		2
Herz,R	1998	+	+	+				+			+		5
Hewett,S	1996	+	+								+		3
Hewitt,K	1991	+	+				+	+					4
Himori,N	1991	+						+					2
Hoffman,C	1995	+	+					+					3
Huang,Q	1994	+		+				+					3
Ikonomidou,C	1989	+	+				+	+					4
Ishimaru,H	1997	+	+					+			+		4
Jacobs,O	1994	+						+					2
Kamiya,T	2005	+	+	+				+	+		+		6
Katchman,A	1997	+	+										2
Keana,J	1989	+	+										2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Kim,G	2000	+						+			+		3
Kim,W	1999	+	+										2
Kimura,M	1998	+	+										2
Kinouchi,H	1994	+	+					+					3
Kohmura,E	1990	+	+										2
Kolko,M	2002	+	+								+		3
Kolko,M	2002	+	+		+						+		4
Kubo,T	2001	+	+								+		3
Kudo,M	2001	+	+					+			+		4
Kunimatsu,T	2001	+	+					+			+		4
Kwon,Y	2000	+	+					+			+		4
Laake,J	1999	+	+										2
Lee,Y	2004	+	+								+		3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Lees,G	1995	+						+			+		3
Lehmann,A	1992	+						+					2
Liniger,R	2001	+	+				+	+			+		5
Lippert,K	1994	+	+	+				+					4
Lippert,K	1994	+	+					+					3
Lippert,K	1994	+	+	+									3
Lobner,D	1990	+	+										2
Lobner,D	1993	+	+								+		3
Loscher,W	1998	+		+			+	+					4
Luque,J	2001	+									+		2
Lustig,H	1992	+											1
Lysko,P	1992	+	+					+					3
Lysko,P	1992	+	+										2
Ma,X	2002	+	+										2

Author	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*Quality Score*
Mabuchi,T	2001	+	+				+	+					4
Mabuchi,T	2001	+	+										2
Margaill,I	1996	+	+	+				+			+		5
Marino,S	2007	+	+								+		3
Massieu,L	2000	+						+			+		3
Matsumoto,M	1992	+	+	+	+			+			+		6
Matsumoto,Y	2004	+	+					+			+		4
Maus,M	1999	+	+										2
McDonald,J	1989	+						+					2
Meloni,B	2002	+	+										2
Milusheva,E	2003	+	+					+			+		4
Monnerie,H	2003	+	+										2
Morioka,M	1995	+	+										2
Moudy,A	1994	+					+						2

Author	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*Quality Score*
Muir,J	1996	+	+										2
Nellgard,B	1991	+	+	+				+			+		5
Nellgard,B	1992	+	+	+			+	+			+		6
Newell,D	1990	+	+				+						3
Newell,D	1995	+	+										2
Newell,D	1995	+	+								+		3
Obrenovitch,T	1997	+	+					+			+		4
Oliveira,I	2002	+	+								+		3
Olney,J	1989	+	+				+	+					4
Ozben,T	2005	+						+			+		3
Ozyurt,E	1988	+	+	+			+	+					5
Pang,Z	1997	+	+										2
Pang,Z	2003	+	+										2
Paquet-Durand,F	2004	+	+										2

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Park,C	1988	+		+			+					+	4
Park,C	1988	+	+	+			+					+	5
Park,C	1989	+	+	+				+					4
Pauwels,P	1989	+	+										2
Pearlstein,R	1998	+	+								+		3
Pocock,J	1998	+	+										2
Prehn,J	1993	+	+	+				+					4
Pringle,A	1997	+	+										2
Pulsinelli,W	1993	+	+	+			+		+				5
Regan,R	1996	+											1
Remblier,C	1999	+	+					+					3
Robert,F	2002	+									+		2
Robertson,S	1997	+	+	+				+					4
Rogers,B	1989	+						+					2

Author	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*Quality Score*
Rudolph,J	1997	+	+										2
Saez-Valero,J	2003	+	+										2
Sarraf-Yazdi,S	1998	+	+	+	+		+	+			+		7
Schulz,J	1995	+	+				+	+					4
Schurr,A	1995	+	+										2
Serteser,M	2002	+	+					+					3
Sheardown,M	1993	+	+				+	+					4
Shirotani,T	1994	+	+					+	+				4
Speliotes,E	1994	+	+				+						3
Stevens,M	1990	+	+	+				+					4
Strasser,U	1995	+	+										2
Streit,W	1992	+	+					+					3
Sturm,C	1993	+											1
Sullivan,B	2002	+	+					+					3

Author	Year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)	(10)	(11)	Quality Score
Thatcher,N	1999	+											1
Veldhuis,W	2003	+	+					+			+		4
Velly,L	2003	+	+								+		3
Volbracht,C	2006	+	+								+		3
Vornov,J	1995	+	+										2
Wahlestedt,C	1993	+	+					+	+				4
Weaver,C	1998	+	+				+						3
Wenk,G	1995	+						+					2
Whishaw,I		+	+										2
Whittingham,T	1992	+											1
Xue,D	1994	+	+	+			+	+	+		+		7
Yamada,K	1997	+	+					+					3
Yamada,Y	1994	+	+										2
Yamashita,K	1996	+	+	+				+					4

Author	*Year*	*(1)*	*(2)*	*(3)*	*(4)*	*(5)*	*(6)*	*(7)*	*(8)*	*(9)*	*(10)*	*(11)*	*Quality Score*
Yao,H	1993	+	+	+				+					4
Yao,H	1994	+	+	+			+	+			+		6
Yoneda,Y	1993	+	+					+			+		4
Zhang,L	1997	+	+					+					3