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Administration of thiazolidinediones for neuroprotection in ischemic stroke; a preclinical systematic review

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Abstract

Thiazolidinediones (TZDs) may prevent or attenuate CNS injury due to an ischemic event. We performed meta-analysis of experimental studies in which a TZD (either rosiglitazone or pioglitazone) was administered in a rodent model of focal or global cerebral ischemia. Infarct volume was the primary endpoint for analysis of drug efficacy, and neurological outcome was also assessed. We identified 31 studies through the use of PubMed and Embase, 22 of which met our pre-specified inclusion criteria and were analyzed with the Cochrane Review Manager software. Treatment with TZDs decreased infarct volume and improved neurological outcome regardless of study quality, dose timing, or ischemia model (transient or permanent). Rosiglitazone and pioglitazone were similarly effective in reducing infarct volume and protecting neurologic function. Importantly, the collective data suggest that pretreatment with a TZD is not required for neuroprotection, although additional studies are clearly needed to define the breadth of the therapeutic window. The data warrant further studies into the potential acute use of TZDs for ischemic stroke therapy in the general population.

Keywords

ischemic stroke; meta-analysis; pioglitazone; rosiglitazone; systematic review; thiazolidinedione

Thiazolidinediones (TZDs), including rosiglitazone and pioglitazone, are FDA-approved insulin-sensitizing agents used in the treatment of type 2 diabetes (Barnett, 2009). These agents were developed as agonists of peroxisome proliferator-activated receptor gamma (PPARγ), a transcription factor involved in regulating cell differentiation and metabolism (Michalik et al, 2006). Patients with diabetes are at high risk of macrovascular events and epidemiological data indicate that pioglitazone reduces the number of macrovascular events including stroke in type 2 diabetic patients (Dormandy et al, 2005). In contrast, similar data on chronic administration of rosiglitazone suggest a modest increase in cardiovascular risk (Nissen and Wolski, 2007; Graham et al, 2010) sufficient to prompt additional safety warnings that are the topic of ongoing controversy[1]. TZDs have also been observed to inhibit inflammation due to ischemia and decrease various inflammatory markers independently of their effects on glycemic control (Luo et al, 2006; Sundararajan et al, 2005). In vitro studies have shown that neuronal PPARγ can contribute to neuroprotection and that TZDs can prevent neuronal apoptosis induced by LPS (Luna-Medina et al. 2005). In response to oxidative injury, pioglitazone decreases COX-2 expression and prevents neuronal death (Zhao 2006). PPARγ ligands reduce the secretion of neurotoxic molecules (i.e. NO, TNF-α, IL-6) that follows macrophage and microglia activation due to ischemia

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[1]http://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/EndocrinologicandMetabolicDrugsAdvisoryCommittee/ucm218491.htm

(Lee 2000, Luna-medina 2005). The in vitro neuroprotective effects of TZDs are linked to increased PPARγ DNA binding and PPARγ antagonists reverse these effects (Zhao 2006b).

Pioglitazone and rosiglitazone are currently being investigated in ongoing as well as closed clinical trials for neuroprotection in patients with type 2 diabetes or metabolic syndrome. In these studies, stroke and cognition are among the endpoint measures (see http://clinicaltrials.gov: clinical trial numbers NCT00095654, Dream Trial Investigators, 2008; NCT00636766, Kadaglou et al, 2010; NCT00212290, NCT00736996; NCT00879970; NCT00242593). In addition, there is an ongoing study of the neuroprotective efficacy of pioglitazone in non-diabetic patients in hemorrhagic stroke (NCT00827892). There is an increased incidence of Alzheimer's Disease in individuals with type 2 diabetes (Craft 2006). This observation has led to pilot studies for the use of pioglitazone in patients with type 2 diabetes and Alzheimer's Disease or mild cognitive impairment (Hanyu et al, 2009). Additional trials are investigating pioglitazone administration in normoglycemic patients with mild cognitive impairment (NCT00242593) and in depressive disorders in individuals with or without diabetes (McIntyre et al, 2007; NCT01109030; NCT00671515, NCT00835120, Kemp et al, 2009; NCT00242619, Rasgon et al, 2010). The anti-inflammatory properties of pioglitazone prompted a pilot study that has reported promising results for its use in multiple sclerosis patients (Shukla et al, 2010; NCT00242177). Further, pioglitazone is currently being tested in a small cohort of Friedreich's Ataxia patients (NCT00811681). However, a trial in amyotrophic lateral sclerosis (NCT00690118) was halted early due to a lack of efficacy at interim analysis.

Thus, the breadth of indications in which TZDs are being tested in humans has broadened beyond insulin resistant, hyperlipidemic conditions. The purpose of this review is to evaluate the preclinical data on the use of rosiglitazone and pioglitazone in stroke models to collectively assess and compare their ability to reduce infarct volume and improve neurological outcome in normoglycemic animals. In particular, we analyze the available preclinical data on the ability of TZDs to provide protection without pretreatment, in order to more aptly address the potential for their acute use in stroke therapy.

Experimental procedures

Study Identification

To identify preclinical studies investigating the use of thiazolidinediones in focal or global cerebral ischemia, literature searches were conducted in PubMed and Embase for all published articles up until July 1st, 2010. Keywords included combinations of thiazolidinedione (TZD), rosiglitazone or pioglitazone with stroke, ischemic brain injury, cerebral ischemia, or middle carotid artery occlusion (MCAO). Reference lists from the resulting publications and reviews were used to identify further relevant publications. To prevent bias, inclusion criteria were pre-specified as the following: (i) experimental ischemic stroke was induced in rodents by transient stroke (transient MCAO or embolic stroke), permanent MCAO, or transient global ischemia (bilateral CAO), (ii) rosiglitazone or pioglitazone was administered, (iii) there was no administration of other agents with potentially neuroprotective effects, (iv) infarct volume was assessed, and (v) a control group was included in the study design. Unlike infarct volume, assessment of neurological outcome was not required for inclusion in this study, but was evaluated as an outcome measure in studies also reporting infarct volume. We chose to only evaluate studies of rosiglitazone and pioglitazone, as these are currently the only FDA-approved thiazolidinediones on the market.

Data extraction

Data on infarct size and neurological outcomes from vehicle- and TZD-treated animals were extracted from all included studies. The effects of rosiglitazone and pioglitazone treatment on infarct volume and neurological deficits were compared to control groups of animals treated with vehicle prior to, during, or after induction of cerebral ischemia. Extracted data included the mean infarct size (expressed as mm^3 or percent of normal brain) or mean neurological score. In addition to the mean values, the standard deviation and the number of animals per treatment group were also extracted. Many studies had multiple groups to facilitate dose responses or time course evaluations; the data from these experiments were extracted from each group as individual values. Data presented graphically rather than reported in the text were obtained from enlarged versions of the graphs. In all included studies, edema was measured and was reported as not significant or was used to correct for infarct volume. Data for neurological outcome were extracted from various neurological tests including: (i) neurological score (subjective sensory motor assessment), (ii) modified limb placement test, (iii) rotarod latency, (iv) tightrope test for forelimb and hindlimb grasping, (v) paw placement cylinder test, (vi) wire hang test, (vii) adhesive tab removal, and (viii) incline test, as documented in Table I. If ischemic duration was insufficient to induce a loss in neurologic function in a particular test, the data were not included. Data were not extracted if mean neurologic scores were not reported (i.e. if only median and confidence intervals were given).

An eight-point scale was used to determine the quality of each of the included studies based on their stated methodology (Gibson et al, 2008). Written evidence was required in order for a study to receive one point in each of the following categories: randomization of treatment groups, assessment of physiological measurements, dose-response evaluation, time course for treatment, investigator blinding, outcome measurements at days 1-3, outcome measurements beyond day 3, and measurement of both infarct size and neurological outcome.

Data analysis

Cochrane Review Manager (version 5) and the statistical package therein (fixed effect model) was used to analyze the extracted data. A one-way ANOVA with a post hoc Bonferroni test was used to determine statistically significant effects among the routes of drug administration. The standardized mean difference was calculated and applied to assess the effect of rosiglitazone and pioglitazone on infarct volume or neurological outcome compared to vehicle treated controls. By this method, the difference between each control and treatment group is divided by the standard deviation of the data. This accounts for the fact that measurements may have been taken differently in each experiment (i.e. mm^3 vs. percent for infarct volume and neurological score vs. other tests for neurological outcome) and that different animal models may have been employed. Statistical heterogeneity was accounted for through the use of the DerSimonian and Laird (1986) pooling model of random effects. The experiments were grouped and analyzed based on (i) outcome (infarct volume or neurological deficits), (ii) methodological quality, (iii) type of TZD administered (rosiglitazone or pioglitazone), (iv) timing of first dose (prior to or following ischemia), or (v) type of model (transient or permanent). For those tests in which an increase in nominal value represented an improvement in outcome (for instance, in the wire hang test), the inverse of the extracted data was used for data comparisons.

Results

Design of Studies

Based on our search criteria, we identified 31 studies that investigated the use of TZDs in an animal model of cerebral ischemia. The earliest study was published in 2004 (Shimazu). Seven of these studies were excluded because they did not measure infarct volume and one study was excluded because the injury model was traumatic brain injury rather than focal or global ischemia (Yi et al, 2008). Out of the final 22 included studies (Table I; Allahtavakoli et al 2006,2007,2009;Fatehi-Hassanabad & Tasker, 2010; Glatz et al, 2010; Ji et al, 2009;Lee et al, 2009;Luo et al, 2006; Nategh et al 2010; Pereira et al, 2006;Schmerbach et al, 2008;Schock et al, 2008; Shimazu et al, 2004; Sobrado et al, 2009;Sundurarajan et al, 2005;Tureyen et al, 2007;Victor et al, 2006;Wang et al 2009; Wu et al, 2008; Zhao et al, 2005; and Zhao et al, 2006), 15 employed the use of an animal model of transient MCAO, 5 performed studies of embolic stroke (Allahtavakoli et al 2006,2007,2009;Chu et al, 2006, Nategh et al 2010; and Wang et al 2009) and 2 used transient bilateral carotid artery occlusion (Fatehi-Hassanabad and Tasker, 2010; Wu et al, 2008).

All studies compared administration of either rosiglitazone or pioglitazone to a vehicle-treated group of animals and measured mean infarct volume in mm^3 or as a percent of either total brain volume or the control hemisphere. The included studies came from 19 independent research groups and data were analyzed from 1348 experimental subjects for infarct volume measurements. Ten of the included studies, from nine independent groups, included measurements of neurological function in 939 experimental subjects. Experimental models for assessment of neurological outcome included subjective neurological scoring as well as objective tests for motor and sensory performance (Table I).

Male rat models (Wistar, Sprague-Dawley, Fisher, Long Evans) were used in 17 of the studies while the remaining 5 used male mouse models (C57BL/6, CD1, 129/SV), though primary data on infarct volume and neurological outcome may not have been measured or reported from all of the included animal models (Table 1). In 18 of the studies the TZD was administered either orally or intraperitoneally. Four studies administered the TZD intracerebroventricularly using Alzet pumps while one mixed the drug into peanut butter (Shimazu et al, 2004). The timing of the first dose ranged from 2 weeks prior to ischemic insult to 1 day following injury. Fourteen studies began administration of the drug prior to injury while 10 started treatment with the TZD either at the time of ischemia or thereafter. Rosiglitazone was administered in 13 of the studies and pioglitazone was used in the remaining 9 studies (Table I).

Overall Efficacy of Drug Treatment

There was a significant protective effect of TZD treatment on infarct size (1.54, 1.40 to 1.68, $p<0.00001$) and neurological outcome (1.19, 1.04 to 1.34, $p<0.00001$) across all models (Figure 1). The nature of this statistical approach is to compare the standardized mean difference between drug treatment and vehicle across all studies. A standardized mean difference of zero represents a lack of drug effect, whereas a positive value indicates a beneficial effect, and a negative mean difference reflects a detrimental effect of the drug.

Reported study quality

The quality scores ranged from 1-8 with a mean of 4.3. Analysis of studies based upon individual quality scores was not very meaningful as scores unevenly distributed over the scoring range; for instance, no studies had a quality score of 3 or 7. Therefore, data from experiments with a study quality of 1-4 were grouped together and compared to those with a study quality of 5-8. Infarct volume was reduced to a similar degree regardless of study

quality (χ^2=1.91, df=1, p=0.17). However, studies with a quality rating of 1-4 were less likely to show efficacy of TZD treatment for improvements in neurological outcome than those with a study quality of 5-8 (χ^2=14.01, df=1, p<0.0002).

Benefits of rosiglitazone vs. pioglitazone

Rosiglitazone and pioglitazone were analyzed separately for their effects on infarct volume and neurological deficits (Fig. 3). Rosiglitazone significantly decreased lesion volume (effect size=1.55, C.I.=1.39 to 1.72, p<0.00001) and improved neurological outcome (1.19, 0.99 to 1.38, p<0.00001). Pioglitazone also reduced lesion size (1.50, 1.24 to 1.76, p<0.00001) and improved neurological outcome (1.2, 0.95 to 1.44, p<0.00001). There was no difference in the effectiveness of the two different drugs with regard to either infarct volume (χ^2=0.12, df=1, p=0.73) or neurological deficits (χ^2=0.00, df=1, p=0.95).

Efficacy of TZD depending on first dose timing

TZD treatment was effective at reducing lesion volume and improving neurological outcomes when dosed prior to or after the induction of focal or global ischemia (Fig. 4). When dosed before ischemic injury, TZDs decreased infarct size (1.56, 1.36 to 1.76, p<0.00001) and improved neurological outcomes (1.12, 0.96 to 1.29, p<0.00001). Administering TZDs at or after the induction of ischemic stroke was also effective in reducing lesion volume (1.52, 1.32 to 1.72, p<0.00001) and improving neurological outcomes (1.73, 1.26 to 2.19, p<0.00001). There was no difference in lesion volume reduction due to dose timing (χ^2=0.08, df=1, p=0.78). Treatment with a TZD after the onset of ischemic injury resulted in a greater improvement in neurological outcomes than did dosing prior to ischemia (χ^2=5.82, df=1, p=0.02).

Effect of TZD on infarct size depending on drug and timing of first dose

Though there were no statistically significant differences in anatomical outcome measures based on the timing of the first dose or the type of TZD administered (rosiglitazone or pioglitazone), there was a difference in effect when the data was analyzed separately for each of the two drugs based on dose timing (Fig. 5). The effects of rosiglitazone on the reduction of lesion size were similar whether it was administered before or after ischemia (χ^2=1.33, df=1, p=0.25). Pioglitazone was more effective at reducing lesion volume when administered before the induction of focal or global ischemia (χ^2=5.93, df=1, p=0.01).

Drug effects based on model

All of the included studies employed a model of either transient or permanent ischemia. TZD treatment in transient ischemia models led to improvements in lesion size (1.51, 1.36 to 1.65, p<0.00001) and neurological outcome (1.17, 1.01 to 1.34, p<0.00001) (Fig. 6). The administration of rosiglitazone or pioglitazone was also effective in permanent ischemia models at reducing infarct volume (2.00, 1.40 to 2.60, p<0.00001) and neurological impairments (1.36, 0.84 to 1.87, p<0.00001). There were no significant differences in either outcome measure comparing permanent versus transient ischemia models (infarct volume: χ^2=2.43, df=1, p=0.12; neurological outcome: χ^2=2.09, df=1, p=0.15).

Effect size according to route of drug administration

The effects of TZDs on anatomic and neurological outcomes significantly differed based on the route of drug administration (Fig. 7). Dosing the TZD by oral gavage tended to be less effective at reducing infarct volume than intraperitoneal (p<0.05), intracerebroventricular (p<0.05), or food-based administration (NS). Conversely, for neurologic outcome, the efficacy according to route of administration was highest with peroral, followed by intraperitoneal and intracerebroventricular delivery (p<0.05 between all groups).

Discussion

The results of this meta-analysis suggest that rosiglitazone and pioglitazone are effective agents for reducing infarct volume and improving neurologic outcome in rodent models of stroke. In the available data, the two drugs were similarly neuroprotective, and more importantly, the protective effects were retained regardless of the timing of the first dose of drug (Table I).

Whereas the effects of TZD treatment on infarct volume were independent of first dose timing, the improvement in neurological outcome was greater when drug was given during or following the ischemic insult (Fig. 4). Although there may be multiple explanations, it is possible that TZDs independently affect sensory/motor coordination in a manner that is influenced by the timing of the dose and/or the cumulative dose. At the time of behavioral assessment, the cumulative dose in the periphery would likely be lower with post-ischemic administration that with pretreatment. The possibility that effects in the periphery are influencing performance in the behavioral tests is supported by the data in Figure 7 that documents the diminished benefit to neurologic outcome when drug is administered intracerebroventricularly.

An advantage of considering TZDs for acute stroke therapy is that these are currently clinically used drugs for which the pharmacokinetics and toxicity are generally well studied. With longer term use, there are issues with these compounds with regard to tolerability, and repeated use is associated with significant undesirable side effects, including weight gain and edema. These shortcomings would unlikely compromise the ability to utilize the compounds acutely for the treatment of stroke, as only short term dosing might be required. The issue with regard to potential cardiovascular risk of rosiglitazone might also be obviated, but this would require further consideration.

Mechanistically, the efficacy of TZDs in stroke models has been attributed to a variety of effects, including their broad anti-inflammatory properties involving induction of antioxidant enzymes, suppression of proinflammatory cytokines, iNOS, COX-2, and adhesion molecules, decreased macrophage infiltration, and promotion of neovascularization (Culman et al, 2007; Chu et al, 2006). There is significant evidence that protection involves activation of PPARγ, at least in part (Glatz et al, 2010; Lin et al, 2006; Luo et al, 2010; Pereira et al, 2006; Schock et al, 2008; Sobrado et al, 2009; Tureyen et al, 2007; Victor et al, 2006; Wu et al, 2009; Zhao et al, 2006), but there is also data suggesting that non-PPARγ-mediated mechanisms specifically at mitochondria may be involved in the mechanism of action of thiazolidinediones (Feinstein et al, 2005). Whether the higher affinity of rosiglitazone for PPARγ (Feinstein et al, 2005) is what allows for administration of generally lower concentrations than pioglitazone (Table I) remains unclear.

Although promising, the data indicate that additional studies are required to determine the efficacy of delayed administration of TZDs (i.e. 6 hrs or longer) and assess outcome measures at delayed time points (i.e. longer than 72 hours, as reported in Chu et al., 2006; Fatehi-Hassanabad & Tasker, 2010; Luo et at., 2006; Sundararajan et al., 2005). Additional studies should take into consideration other variables as suggested by Howells et al (2010) that may strengthen the rationale and guide plans for testing in the clinical setting. Some of these variables were broached in the current studies, such as testing in the context of co-morbidities, including hypertension and diabetes (Tureyen et al, 2007) or tPA treatment (Wang et al, 2009) and elevated temperature (Nategh et al, 2010). In each of these studies, TZD treatment was neuroprotective. Of note, most studies that tested delayed administration of TZD from 4 to 24 hours (Allahtavakoli et al 2006, 2009; Ji et al 2009; Tureyen et al, 2007; Wang et al, 2009) found protective effects of rosiglitazone. In the single study that

tested delayed (24 hr) administration of pioglitazone with assessment at 6 weeks (Ji et al, 2009), treatment was no longer as effective as it had been at an earlier point of evaluation, but these observations need to be strengthened with further studies. Overall, current data are supportive that thiazolidinediones could be effective agents in the acute treatment of ischemic stroke.

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Abbreviations used

MCAO	middle carotid artery occlusion
PPARγ	peroxisome proliferator-activated receptor gamma
TZD	thiazolidinedione

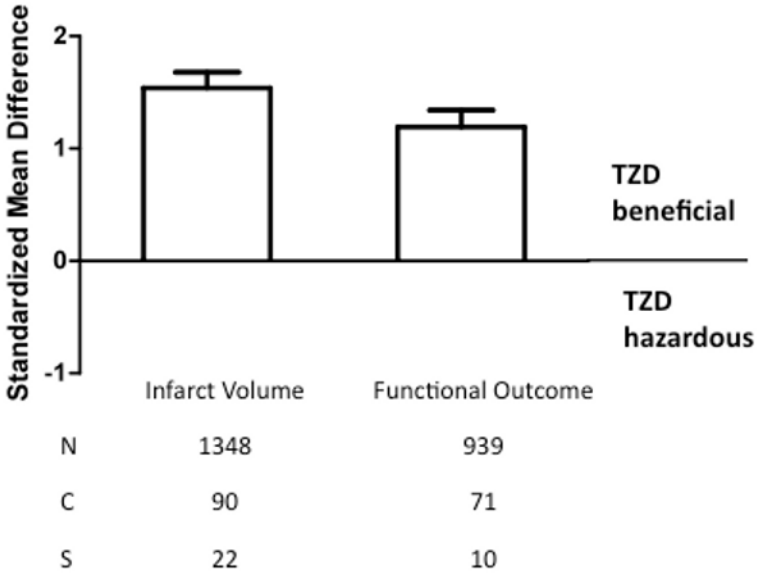

Fig. 1.

Standardized mean difference and 95% confidence interval by outcome measure. A beneficial effect of TZD (rosiglitazone or pioglitazone) was detected on infarct size and neurologic function ($p<0.00001$) as reported in the publications listed in Table I. N=number of animals; C=number of comparisons; S=number of published studies.

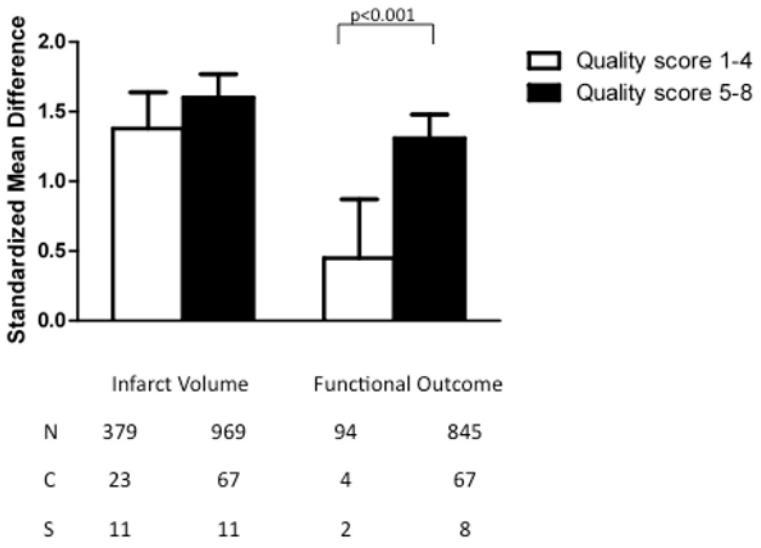

Fig. 2.

Standardized mean difference and 95% confidence interval by outcome measure with subcomparison by study quality score, assigned as described in the text. A beneficial effect was detected on both infarct size and neurologic function, although lower study quality was associated with a smaller effect size on neurologic outcome ($p<0.002$). N=number of animals; C=number of comparisons; S=number of published studies.

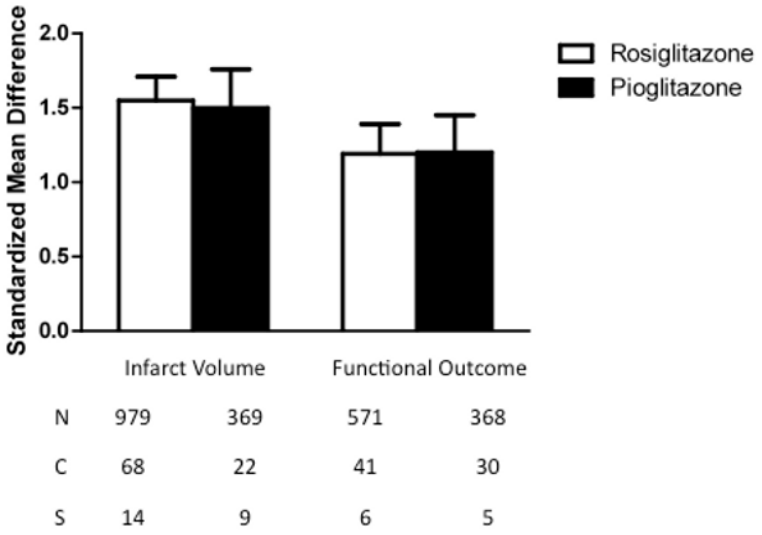

Fig. 3.

Standardized mean difference and 95% confidence interval by outcome measure with subcomparison of the two thiazolidinediones under consideration, rosiglitazone versus pioglitazone. The drugs were similarly protective to both infarct size and neurologic function ($p<0.00001$). N=number of animals; C=number of comparisons; S=number of published studies.

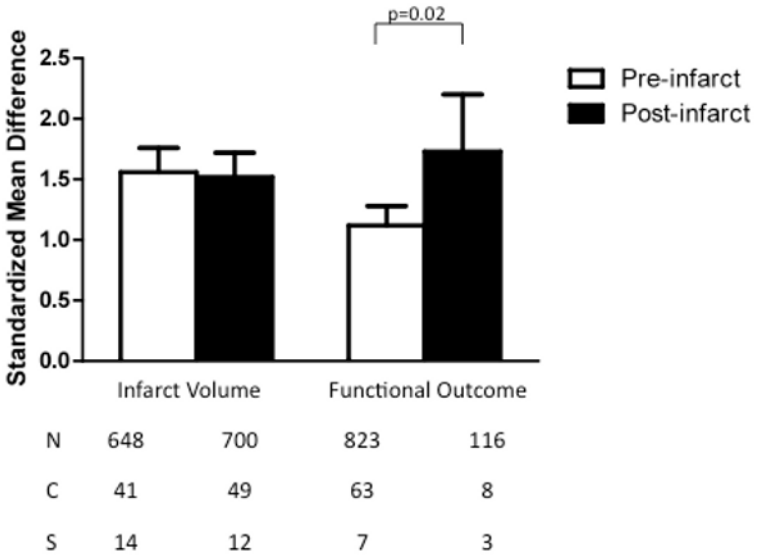

Fig. 4.

Standardized mean difference and 95% confidence interval by outcome measure with subcomparison of dose timing, either pre-treatment or treatment at the time of initiation of ischemia or any time thereafter, as indicated in Table I. Infarct size was independent of dose timing ($p<0.00001$). However, drug administration at or following the time of ischemia was more effective than with pre-treatment ($p=0.02$). N=number of animals; C=number of comparisons; S=number of published studies.

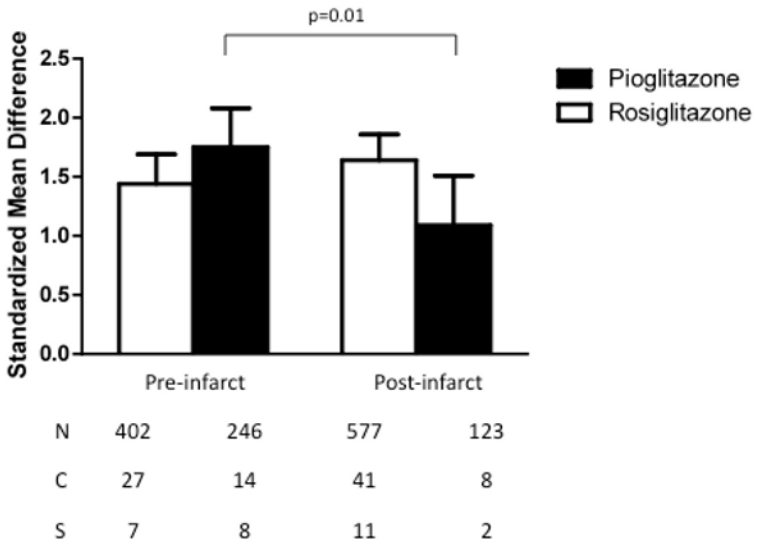

Fig. 5.

Standardized mean difference and 95% confidence interval for effects of rosiglitazone or pioglitazone on infarct size with subcomparison of dose timing, either pre-treatment or treatment at the time of initiation of ischemia or any time thereafter, as indicated in Table I. Although rosiglitazone was similarly protective with pre-versus post-treatment, pioglitazone was more effective when administered before rather than after the induction of either focal or global ischemia (p=0.01). N=number of animals; C=number of comparisons; S=number of published studies.

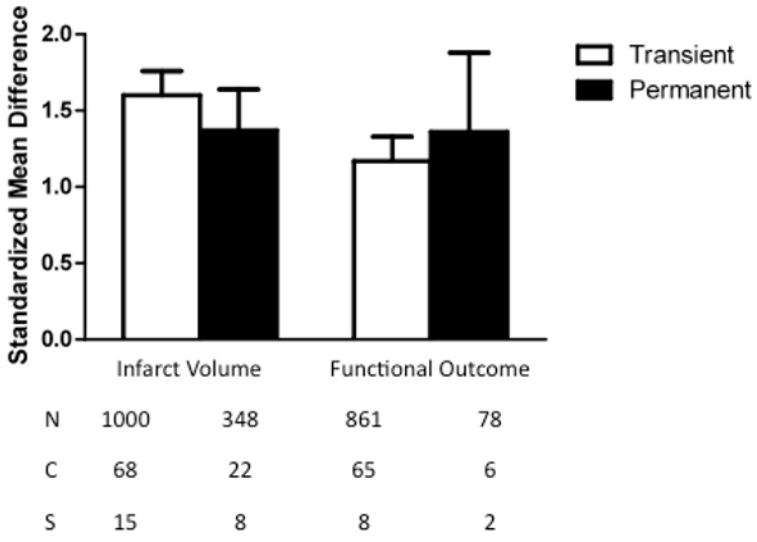

Fig. 6.

Standardized mean difference and 95% confidence interval by outcome measure with subcomparison of transient versus permanent ischemia model. Infarct size and neurologic function were similarly effective in both types of ischemia models ($p<0.00001$). N=number of animals; C=number of comparisons; S=number of published studies.

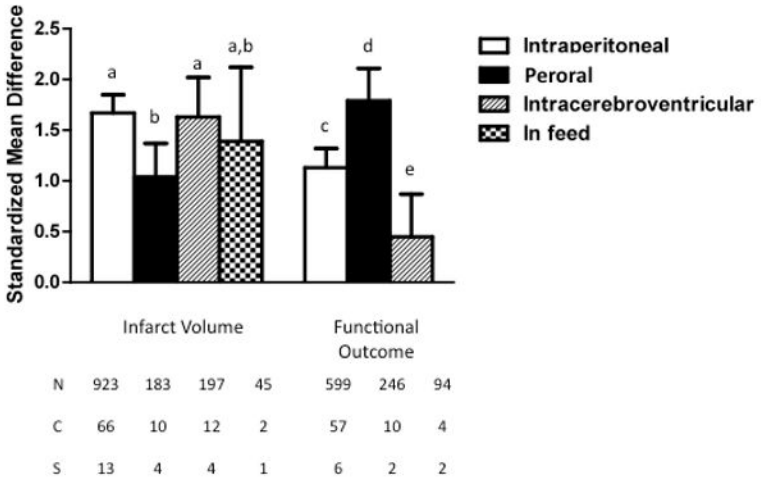

Fig. 7.

Standardized mean difference and 95% confidence interval by outcome measure with subcomparison of route of drug administration. Post-hoc analysis was performed by outcome measure, and bars with same letter were statistically similar to one another. Thus, administration by oral gavage (peroral) was less effective at decreasing infarct volume than i.p. or i.c.v. administration, and efficacy of TZD in preserving neurologic function was greatest with peroral administration, followed by i.p. administration, and was least effective with i.c.v. drug delivery. ($p<0.05$). N=number of animals; C=number of comparisons; S=number of published studies.

Table I

Characteristics of studies included in the review

Study	Parameters assessed[1]	TZD (dose)	First dose timing	Species[2]	Model[3]	Route of drug administration[4]
Allahtavakoli et al., 2006	infarct volume, % (48h)	Rosi (0.033, 0.1, 0.3, 1mg/kg)	-1h, 0h,or+4h	Male WR	embolic stroke	i.p.
Allahtavakoli et al., 2007	infarct volume, % (48h)	Rosi (0.1 mg/kg)	Oh	Male WR	embolic stroke	i.p.
Allahtavakoli et al., 2009	infarct volume, % (72h)	Rosi (5 mg/kg)	+24h	Male WR	embolic stroke	i.p.
Chu et al.,2006	infarct volume, % (24h); MLPT (1,7,14,21,28,35d)	Rosi (0.3, 3 mg/kg)	-7d	Male SD	MCAO (t) 90 min	p.o.
Fatehi-Hassanabad & Tasker, 2010	infarct volume, % (1,3,7,14d); TT (6,24,72h), PPT & RR (6h,1,3,7,14d)	Rosi (5, 10 mg/kg)	-10min	Male CD1 mice	BCAO (t) 45 min	i.p.
Glatz et al, 2010	infarct volume, mm^3 (24,48h); SSMA (24,48h)	Pio (3nmol/hour)	-6d	Male WR	MCAO (t) 90 min	i.c.v.
Ji et al., 2009	infarct volume, mm^3(72h)	Pio (20 mg/kg)	Oh or+1d	129/SV mice	MCAO (t)	i.p.
Lee et al., 2009	infarct volume, mm^3(24h)	Pio (40 mg/kg/day)	-3d	Male C57BL/6 mice	MCAO (t)	p.o.
Luo et at., 2006	infarct volume, mm^3 (2,7d); SSMA & CT (7d)	Rosi (0.75 -12 mg/kg)	-1h	Male C57BL/6 mice	MCAO (t) 90 min	i.p.
Nategh et al. 2010	infarct volume, %(24h)	Rosi (1mg/kg)	Oh	Male WR	embolic stroke	i.p.
Pereira et al.,2006	infarct volume, mm^3 (48h); SSMA (48h)	Rosi (1-3 mg/kg)	+10min or+2h	Male FR	MCAO (p)	i.p.
Schmerbach et al., 2008	infarct volume, mm^3 (48h); SSMA (24,48h)	Pio (2,20 mg/kg/day)	-5d	Male WR	MCAO (t) 90 min	p.o.
Schock et al., 2008	infarct volume, % (72h)	Rosi (6mg/kg)	Oh	Male mice	MCAO (t) 60 min	i.p.
Shimazu et al., 2004	infarct volume, mm^3 (24h); SSMA-U (24h)	Pio (20 mg/kg/day)	-72h	Male SD	MCAO (t) 90 min, MCAO (p)	feed
Sobrado et al., 2009	infarct volume, mm^3 (48h & 7d); SSMA (48h), WH (48h)	Rosi (1,3 mg/kg)	+10min	Male FR, B6;129F2/J mice	MCAO (p)	i.p.
Sundararajan et al., 2005	infarct volume, % (24h & 22d); SSMA (1-22d), ATR (1-22d), IT(1-22d)	Pio (1mg/kg)	-24h	Male WR Male SD, SHR, C57BL/6, SV129, db/db, S2/SvPasCrl	MCAO (t) 2h	i.p.
Tureyen et al., 2007	infarct volume, mm^3(72h),SSMA (72h)	Rosi, Pio (0.5-6 mg/kg)	-4h through+6h	mice	MCAO (t) 2h	i.p.
Victor et al., 2006	infarct volume, %(24h)	Pio, Rosi (1 & 0.1 mg/kg)	-24h	Male WR	MCAO (t) 2h	i.p.
Wang et al., 2009						
Experiment 1	infarct volume, % (48h); SSMA-U	Rosi (2,10 mg/kg/day)	-2wk	Male WR	embolic stroke	p.o.
Experiment 2	infarct volume, % (48h)	Rosi (2 mg/kg/day)	+1,3, or 6h	Male WR	embolic stroke	p.o.

Study	Parameters assessed[1]	TZD (dose)	First dose timing	Species[2]	Model[3]	Route of drug administration[4]
Wu et al., 2008						
Experiment 1	infarct volume, mm^3(24h)	Rosi (0.2-500 ng)	Oh	Long Evans	BCAO (t) 30 min	i.c.v.
Experiment 2 and 3	infarct volume, mm^3(24h)	Rosi (50ng)	+2h	Long Evans	BCAO (t) 30 min	i.c.v.
Zhao et al., 2005	infarct volume, mm^3 (48h); SSMA (24, 48h)	Pio (3nmol/hour)	-5d	Male WR	MCAO (t) 90 min	i.c.v.
Zhao et al., 2006	infarct volume, mm^3(48hr)	Pio (3nmol/hour)	-5d	Male WR	MCAO (t) 90 min	i.c.v.

[1] MLPT= modified limb placement test; TT = tightrope test for forelimb & hindlimb grasping; PPT= paw placement cylinder test; RR = rotarod latency; CT= Corner Test (no. of left turns); SSMA= subjective sensory motor assessment; SSMA-U = SSMA data was presented, but mean values were not extractable for meta-analysis; WH = wire hang test (latency to fall); ATR = adhesive tab removal; IT = Incline test

[2] WR=Wistar rat; SD=Sprague Dawley rat; SHR=Spontaneously hypertensive rat

[3] MCAO=middle cerebral artery occlusion; BCAO=bilateral carotid artery occlusion; (t)=transient; (p)=permanent

[4] i.p.=intraperitoneaI injection; p.o.=by mouth (oral gavage); i.c.v.= intracerebroventricular injection (by Alzet pump); feed=drug formulated into peanut butter