THIAZOLIDINEDIONES AND ISCHEMIC STROKE (LİTERATURE REVİEW AND REASONİNG FOR THE NEW POTENTİAL TREATMENT APPROACHES)

Lytvynenko N.V., *Delva M.Yu.
Department of neurology with neurosurgery and medical genetic, Ukrainian medical stomatological academy, Poltava, Ukraine

ABSTRACT

Stroke is a leading cause of death and disability among adult population. Many pathological events including inflammation, oxidative stress, and apoptosis contribute to the secondary neuronal death after stroke. The goal of this review is to discuss the therapeutic potential and putative mechanisms of neuroprotective properties of thiazolidinediones (peroxisome proliferator-activated receptors-? agonists) at ischemic stroke. Thiazolidinediones have insulin-sensitizing and other additional pleiotropic properties. Ischemic neuroprotection afforded by thiazolidinediones has been involved anti-inflammatory, anti-oxidant, anti-apoptotic properties, as well as effects on endothelial function and repair. These novel actions of thiazolidinediones could offer some protection against the potentially enhanced damage of brain ischemia in patients with abdominal obesity and insulin resistance and may open new exciting lines of investigation on stroke treatment.

Key words: ischemic stroke, pathogenesis, thiazolidinediones, neuroprotection.

Stroke is one of the leading causes of morbidity and mortality worldwide. In the last 2 decades, there has been an enormous increase in the pathophysiological knowledge of brain ischemia and post-ischemic cerebral processes.

More than 1000 neuroprotective agents that showed beneficial effects in pre-clinical studies failed in clinical trial, displayed severe side-effects or worsened the outcome of stroke. Strategies of proven benefit for acute intervention in stroke are still limited to administration of tissue plasminogen activator within 4.5 h [24], aspirin within 48 h of stroke onset, stroke care unit management, and decompressive surgery for supratentorial malignant hemispheric ischemia [45]. Thus, the dilemma of experimental success and practical failure encourages the search for new applications of already-approved drugs.

Brain injury after an ischemic event is an evolving process that can continue for days after injury. During the delayed post-ischemic phase, which may last for several days or even weeks, secondary phenomena such as inflammation and apoptotic cell death may contribute to further progression of brain injury [25]. Recently, much attention has been drawn to nuclear proteins - peroxisome proliferator-activated receptors (PPARs). PPARs are ligand-activated transcription factors that belong to the nuclear hormone receptor superfamily, structurally similar to steroid hormone receptors [15]. PPARs regulate target genes expression [9]. Most recent discoveries portray PPARs as promising pharmacological targets for the treatment of acute ischemic stroke, thanks to their ability to simultaneously interfere with several mechanisms that underlie the pathophysiology of brain ischemia, thus leading to an interesting protective strategy to counteract the multiple deleterious effects of ischemic and post-ischemic injuries [11]. Three types of PPARs have been identified - alpha, delta/beta and gamma. Each PPAR type regulates activity of definite genes and controls numerous

*e-mail: delwa@mail.ru

processes of cellular metabolism, differentiation, proliferation, apoptosis, etc. There are endogenous (free fatty acids) and synthetic (fibrates, non-steroidal anti-inflammatory drugs, thiazolidinediones) ligands for PPARs [5].

Thiazolidinediones (TZD), glitazones - are full PPAR-y agonists. TZD effects are realized through regulation of genes transcription involved in metabolism of fats, carbohydrates, energy homeostasis, and activity of immune tissues in different organs and systems [5, 6]. TZD have insulin-sensitizing properties in patients with type 2 diabetes or impaired glucose tolerance [5] In addition to their ability to lower insulin levels, TZD increase high density lipoprotein cholesterol levels, decrease serum fatty acid and triglyceride concentrations, minimally reduce blood pressure, enhance fibrinolysis, improve endothelial cell function, decrease vascular inflammation, reduce oxidative stress, etc [28].

Currently, only two TZD: rosiglitazone and pioglitazone are approved for clinical practice. In the contest of cerebrovascular pathology, it's appropriate to underscore some features of these drugs: pioglitazone crosses the blood brain barrier much more easily than rosiglitazone [5]; however, rosiglitazone binds to PPAR-y with ten times more affinity than pioglitazone [50].

TZD are already approved for the routinely management of type 2 diabetes as effective insulin sensitizers of peripheral tissues. However in recent years the breadth of indications in which TZD is being tested in humans has broadened beyond insulin resistance, particularly in neurology: multiple sclerosis, extrapyramidal disorders, Alzheimer's disease, mild cognitive impairments, depressive disorders, etc. In relation to cerebrovascular pathology, there is ongoing study of the neuroprotective efficacy of pioglitazone (30 mg per day) in non-diabetic patients in hemorrhagic stroke (Safety of Pioglitazone for Hematoma Resolution In Intracerebral Hemorrhage; see: number clinical trial (NCT) 00827892) and there is ongoing study which assesses the effects of pioglitazone, once daily on brain hemodynamics in healthy elderly participants (Study to Assess the Effects of Daily Administration of Pioglitazone on Brain Hemodynamics in Healthy Elderly Participants; NCT01456117).

Recent multiple data from animal experiments strongly indicate that TZD confer neuroprotection and neurological improvement following cerebral ischemia. It has been performed meta-analysis of experimental studies in which TZD (either rosiglitazone or pioglitazone) were administered in a rodent model of focal or global cerebral ischemia [48]. There were identified 31 studies that investigated the use of TZD and a vehicle in an animal model of cerebral ischemia, 22 of which met the pre-specified inclusion criteria (measurement of mean infarct volume) and were further analyzed. The included studies came from 19 independent research groups and data were analyzed from 1.348 experimental subjects for infarct volume measurements. 10 of the studies included measurements of neurological function in 939 experimental subjects. In 18 of the studies, TZD was administered either orally or intraperitoneally; 4 studies administered TZD intracerebroventricularly. The timing of the first dose ranged from 2 weeks prior to ischemic insult to 1 day following injury. 14 studies began administration of the drug prior to injury, whereas 10 started treatment with 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.

TZD treatment significantly reduced infarcts sizes by 54% (effect size (ES) 1.54; confidence interval (CI) 1.40-1.68; $p<0,00001$) and improved neurological outcome by 19% (ES 1.19; CI 1.04-1.34; $p<0.00001$) in comparison with vehicle-treated controls. Rosiglitazone and pioglitazone were analyzed separately for their effects on infarct volume and neurological deficits. Rosiglitazone decreased lesion volume by 55% (ES 1.55; CI 1.39-1.72; $p<0.00001$) and improved neurological outcome by 19% (ES 1.19; CI 0.99-1.38; $p<0.00001$).

Pioglitazone also reduced lesion size by 50% (ES 1.50; CI 1.24-1.76; p<0.00001) and improved neurological outcome by 20% (ES 1.2; CI 0.95-1.44; p<0.00001). There was no difference in the effectiveness of the two different drugs with regard to either infarct volume (p=0.73) or neurological deficits (p=0.95).

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. When dosed before ischemic injury, TZD decreased infarct size by 56% (ES 1.56; CI 1.36-1.76; p<0.00001) and improved neurological outcomes by 12% (ES 1.12; CI 0.96-1.29; p<0.00001). Administering TZD at or after the induction of ischemic stroke also reduced lesion volume by 52% (ES 1.52; CI 1.32-1.72; p<0.00001) and improved neurological outcomes by 73% (ES 1.73; CI 1.26-2.19; p<0.00001). There was no difference in lesion volume reduction because of dose timing (p=0.78). Treatment with TZD after the onset of ischemic injury resulted in a greater improvement in neurological outcomes than did dosing prior to ischemia (p=0.02). The effects of rosiglitazone on the reduction of lesion size were similar whether it was administered before or after ischemia (p=0.25). Pioglitazone was more effective at reducing lesion volume when administered before the induction of ischemia (p=0.01). These findings may support the idea that TZD have an extended therapeutic window for the treatment of ischemic stroke, as it targets delayed pathways.

The effects of TZD on anatomic and neurological outcomes significantly differed based on the route of drug administration. Dosing TZD by food-based administration tended to be less effective at reducing infarct volume than intraperitoneal (p<0.05), intracerebroventricular (p<0.05). 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) [48].

This ischemic neuroprotection afforded by TZD has been involved anti-inflammatory, anti-oxidant, anti-apoptotic properties, as well as effects on endothelial function and repair [15].

Post-ischemic cerebral inflammation is essential for necrotic core clearing and formation of gliosis following ischemia [33]. The timing and the level of activation of different inflammatory components define the beneficial versus the damaging effects of local cerebral inflammation [4]. The increased post-ischemic expression of adhesion molecules and selectins on blood vasculature mediates leukocyte-endothelial cell interactions followed by blood brain barrier breakdown and leukocyte infiltration into the brain parenchyma [18, 43]. The infiltrated macrophages and neutrophils activate resident microglia and astrocytes [18]. Following stroke, leukocytes as well as neurons, astrocytes, microglia, and oligodendrocytes generate proinflammatory mediators (cytokines, chemokines, and prostaglandins), free radicals, other neurotoxic substances which exacerbate post-ischemic secondary neuronal death [1, 26].

In experiment pre-treatment as well as post-treatment with rosiglitazone significantly decreased the post-ischemic intercellular adhesion molecule-1 expression and extravasation of macrophages and neutrophils into brain. Moreover, rosiglitazone treatment curtailed the post-ischemic expression of the pro-inflammatory genes interleukin-1?, interleukin-6, macrophage inflammatory protein-1?, monocyte chemoattractant protein-1, cyclooxygenase-2, inducible nitric oxide synthase, early growth response-1, nuclear factor-kappa B in ischemic hemispheres. Rosiglitazone also increased the expression of the anti-inflammatory gene suppressor of cytokine signaling-3 and prevented the phosphorylation of the transcription factor signal transducer and activator of transcription-3 after focal ischemia [46].

Neutrophils are the earliest leukocyte subtype to show substantial up-regulation in gene expression and to infiltrate areas of cerebral ischemia [12]. Compared to the control group, the administration of rosiglitazone, starting

24 h after focal cerebral ischemia prevented neutrophilia in blood ($p<0.005$) 72 h after medial cerebral artery occlusion/reperfusion [2].

In response to ischemic injury, TZD decrease cyclooxygenase-2 expression, reduce the secretion of proinflammatory mediators and neurotoxic molecules (interleukin-1?, interleukin-6, tumor necrosis factor-?, matrix metalloproteinase-9, myeloperoxidase, inducible nitric oxide synthase) in peri-infarct brain areas [7, 31, 34, 44, 51].

TZD affect the generation of radical oxygen species on various levels. These drugs induce the expression of the anti-oxidant enzymes copper/zinc-superoxide dismutase and catalase in affected hemispheres [42, 46]. The treatment of rats with either pioglitazone or rosiglitazone before focal cerebral ischemia decreased the production of radical oxygen species and nitrite, decreased lipid peroxidation and reversed the depleted stores of glutathione [16]. TZD attenuate the expression of inducible nitric oxide synthase in inflammatory cells [44], which is considered to be an important source of the deleterious radical peroxynitrite.

Prevention of apoptosis is one of major mechanisms thought to underlie TZD neuroprotection after ischemic brain injury [20, 21]. Apoptosis may be responsible for up to 50% of cellular deaths after cerebral ischemia [22]. Rosiglitazone treatment resulted in decreased apoptosis, measured as reduction of caspase-3 activity in the ischemic cortex in a rat infarction model [32]. Delayed rosiglitazone therapy (24 h after cerebral ischemia) significantly prevented DNA fragmentation in the cortical area adjacent to the necrotic core, indicating that the relative risk of apoptosis in the control group was more than 8 times higher than in rosiglitazone treated animals [2].

In experimental ischemic strokes it has been demonstrated that rosiglitazone-fed rats showed the increased endothelial nitric oxide synthase expression in vessels of ischemic hemispheres and enhanced angiogenesis around the ischemic margin [13].

So far, there are limited clinical data on TZD use in patients with ischemic strokes.

The use of pioglitazone, as a preventive approach to ischemic brain injury has been recently addressed by two large clinical trials: the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROactive) and the Insulin Resistance Intervention after Stroke (IRIS). The PROactive trial randomized 5238 patients with type II diabetes and a history of macrovascular disease to the pioglitazone (15-45 mg per day) or placebo. The average time of observation was 34.5 months. The PROactive study has demonstrated that pioglitazone significantly reduces the combined risk of heart attacks, strokes and death by 16% in high risk patients with type 2 diabetes (hazard ratio (HR) 0.84; 95% CI, 0.72-0.98; $p<0.03$) [19]. Moreover, in a subgroup analysis of PROactive study, pioglitazone reduced the risk of a recurrent stroke by 47% (HR 0.53; 95% CI, 0.34-0.85; $r=0.0085$) [49]. However, it remains unclear whether the suggested beneficial effects of pioglitazone secondary stroke prevention are mediated by insulin sensitization or by additional observed reductions in risk factors, such as arterial hypertension and dyslipidemia. This question and that related to the potential beneficial effects of pioglitazone in non-diabetic patients with stroke will be addressed by the IRIS trial (NCT00091949), a randomized trial on more than 3000 non-diabetic subjects who are insulin resistant and have had a recent transient ischemic attack or ischemic stroke. The IRIS study began on February 2005 and it is still recruiting patients.

In the Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone (CHICAGO) trial, which involved 462 patients with type 2 diabetes (most of whom had no history of cardiovascular disease), pioglitazone 15-45 mg/day (over 18 months) significantly slowed the progression of carotid intima-media thickness, a validated measure of atherosclerosis progression [36].

Researches from Yale University School of

Medicine had determined the effectiveness of pioglitazone (45 mg per day) compared with placebo for improving insulin sensitivity among non-diabetic patients with a recent transient ischemic attack or non-disabling ischemic stroke and impaired insulin sensitivity. Patients assigned to pioglitazone (n=10) and placebo (n=10) were similar in insulin sensitivity, age and obesity. The mean proportional increase in insulin sensitivity was 62% among patients assigned to pioglitazone compared with a 1% decline among patients assigned to placebo ($p<0.001$). Thus, pioglitazone is effective for improving insulin sensitivity among patients with recent ischemic episodes and impaired insulin sensitivity [29].

In a controlled study 30 stroke patients with type II diabetes, admitted for acute inpatient stroke rehabilitation, receiving pioglitazone or rosiglitazone were matched for age, sex, functional disability and interval post-stroke with 30 stroke patients with type II diabetes not receiving TZD. Use of TZD was associated with enhanced functional recovery ($p=0.015$) [30].

Interestingly, high plasma levels of 15-delta-prostaglandin J2 (endogenous PPAR-? agonist, which share neuroprotective effects of TZD in experimental models of ischemic stroke [38]) have been associated with good neurological outcome and smaller infarct volume in patients with an acute atherothrombotic stroke [8].

Thus, TZD may be associated with beneficial effects after cerebral ischemia in patients with insulin resistance. On the other hand, it is well known, abdominal obesity in most cases is associated with insulin resistance and lipotoxicity.

Most of the research about the obesity and cerebrovascular disease has been restricted to the field of stroke prevention. However, some of the metabolic abnormalities and risk factors that integrate the lipotoxicity have been associated with a worsening of stroke outcomes. In this context, obesity-related alterations, as components of metabolic syndrome, comprise impairment in the endogenous fibrinolytic capacity, hyperglycemia, endothelial dysfunction, chronic endothelial damage, and a proinflammatory state, all of which may contribute to amplify cerebral ischemic damage and to hamper arterial recanalization [3].

Recently it has been found that obesity increases severity of strokes and may determine the clinical course of diseases. Elevated body mass index is associated with a lower likelihood of being discharged home and a trend toward extended hospital stay among patients hospitalized for ischemic stroke [39]. Functional state (according to Barthel index) of the subjects with obesity/overweight at discharge from hospital after ischemic strokes was actually worse in comparison to the subject with the normal weight [40]. We have identified that abdominally obese patients with cerebral infarction volumes more than 20 cm3 (according to MRI investigation), have more severe clinical course of ischemic strokes according to NIHS scale, slower regression of neurological symptoms and worse functional outcomes according to modified Rankin scale in comparison with normal weight patients [52].

TZD decrease the expression of lipotoxic adipokines and increase the level of circulating adiponectin [10, 47]. For example, Japanese researches examined short-term effects of pioglitazone (30 mg per day) on serum adiponectin in non-diabetic subjects with normal glucose tolerance. Adiponectin level rapidly and reliably ($p<0.05$) increased within 3 days of pioglitazone treatment in all subjects and continued to increase throughout the study; moreover, decrease in leptin levels were detected after 14 days, but it was not statistically significant [27]. In the double-blind, randomized, controlled trial it has been determined the effects of pioglitazone (30-45 mg per day for duration of 6 months) in healthy, abdominally obese men and women. Serum adiponectin levels rose sharply ($p<0.001$) in the treatment groups. A significant positive correlation was observed between the change of the adiponectin levels and subcutaneous fat [41].

Which adverse side-effects of TZD must be taken into consideration? These drugs cause an

increase in body weight, hemodilution, peripheral edema, and deterioration of cardiomyopathies. Pioglitazone can produce slight weight gain, in some studies average of 3 kg. [14]. However, it has been found that TZD redistribute of fat in favor of subcutaneous fraction by reducing the amount of visceral fraction [17]. As is known, just visceral fat is associated with insulin resistance and lipotoxicity.

Fluid retention manifests as peripheral edema occurs in 4% to 6% of patients treated with TZD. Peripheral edema may worsen existing heart failure or cause new onset heart failure. However, randomized controlled trials have clearly shown increased rates of hospitalization for heart failure due to TZD, but not increased mortality [35].

Rosiglitazone is thought to be related to bone fractures in postmenopausal women by suppressing osteoblastogenesis (bone formation) and stimulating osteoclastogenesis (bone resorption) [23].

One meta-analysis of 42 randomized trials involving 27.000 patients demonstrated that rosiglitazone is associated with the increase in the risk of myocardial infarction by 43% (HR 1.43; 95% CI, 1.03-1.98; p=0.03) [37]. In 2010, an FDA advisory panel voted to keep rosiglitazone on the market, albeit with a tougher warning (drug must be used with increased caution in ischemic heart disease).

These, however, are long-term side effects and should not compromise the short-term TZD application after stroke, which might be sufficient for improved neurological outcome. In addition, it should be noted that TZD do not increase insulin levels, and hence they are less likely to lead to a hypoglycemic state [14].

CONCLUSIONS. Although clinical data are limited, a wide array of evidence obtained in animal models now shows that TZD treatment may be a rational and effective strategy against ischemic brain damage. The beneficial effects of TZD in experimental models of stroke are mediated by different mechanisms, as expected based on their pleiotropic pharmacological profile. Taken together, these novel actions of TZD could offer some protection against the potentially enhanced damage of brain ischemia in patients with abdominal obesity and insulin resistance and may open new exciting lines of investigation on stroke treatment.

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РЕЗЮМЕ

ТИАЗОЛИДИНДИОНЫ И ИШЕМИЧЕСКИЙ ИНСУЛЬТ

Литвиненко Н.В., Дельва М.Ю.
Кафедра нервных болезней с нейрохирургией и медицинской генетикой
Украинская медицинская стоматологическая академия, Полтава, Украина

Инсульт является одной из ведущих причин смертности и инвалидности среди взрослого населения. Обзор литературы посвящен анализу экспериментальных и клинических данных о влиянии тиазолидиндионов (лекарственных препаратов - агонистов гамма-рецепторов, активирующих пролиферацию пероксисом) на развитие и течение ишемических инсультов. Тиазолидиндионы рутинно применяются в лечении сахарного диабета, как сенситизаторы периферических тканей к инсулину. Кроме того, тиазолидиндионы обладают дополнительными плейотропными свойствами. Современные научные исследования доказывают наличие противовоспалительных, антиоксидантных и антиапоптозных эффектов у тиазолидиндионов при постишемических церебральных поражениях. Терапия тиазолидиндионами может рассматриваться как потенциальное средство патогенетического лечения постишемических церебральных нарушений у пациентов с абдоминальным ожирением и инсулинорезистентностью. Однако, для окончательного выяснения краткосрочных и долгосрочных эффектов тиазолидиндионов при ишемических инсультах необходимо проведение рандомизированных исследований.
Ключевые слова: ишемический инсульт, патогенез, тиазолидиндионы, нейропротекция.

XÜLASƏ

TİAZOLİDİNDİONLAR VƏ İŞEMİK İNSULT

Litvinenko N.V., Delva M.Yu.
Neyrocərrahiyyə və tibbi genetika ilə birgə sinir xəstəlikləri kafedrası
Ukrayna tibbi stomatoloji akademiya, Poltava, Ukrayna

İnsult yaşlı əhali arasında ölüm və əlilliyin aparıcı səbəblərindən biridir. Ədəbiyyat icmalı tiazolidindionların (peroksisomun proliferasiyasını aktivləşdirən qamma reseptorların aqonistləri) işemik insultların inkişafı və gedişinə təsiri haqda eksperimental və kliniki məlumatların analizinə həsr edilib. Tiazolidindionlar şəkərli diabetin müalicəsində periferik toxumaların insulinə qarşı həssaslığını artırmaq üçün rutin olaraq istifadə olunur. Bundan başqa tiazolidindionlar əlavə olaraq pleyotrop xüsusiyyətlərə malikdir. Müasir elmi tədqiqatlar tiazolidindionların postişemik serebral zədələnmələr zamanı iltihabəleyhi, antioksidant və antiapoptoz effektlərə malik olmasını sübut edir. Tiazolidindionlar abdominal piylənmə və insulinə qarşı rezistentliyi olan xəstələrdə postişemik serebral zədələnmələrin patogenetik müalicəsi üçün potensial vasitə ola bilər. Amma tiazolidindionların işemik insultlar zamanı tez və gecikmiş effektlərini tam öyrənmək üçün, randomizəolunmuş tədqiqatların aparılması vacibdir.

Açar sözlər: işemik insult, patogenez, tiazolidindionlar, neyroproteksiya.

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