**Name of journal: World Journal of Diabetes**

**ESPS Manuscript NO: 5387**

**Columns: FIELD OF VISION**

**Antidiabetic treatment and stroke severity and outcome**

Magkou D *et al*. Antidiabetic treatment and stroke severity and outcome

Dimitra Magkou, Konstantinos Tziomalos

**Dimitra Magkou, Konstantinos Tziomalos,** First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, Thessaloniki 54636, Greece

**Author contributions:** Magkou D drafted the paper; Tziomalos K revised the draft critically for important intellectual content.

**Correspondence to: Konstantinos Tziomalos, MD, PhD,** First Propedeutic Department of Internal Medicine, Medical School, Aristotle University of Thessaloniki, AHEPA Hospital, 1 St. Kyriakidi, Thessaloniki 54636, Greece. [ktziomalos@yahoo.com](mailto:ktziomalos@yahoo.com)

**Telephone:** +30-2310-994621 **Fax:** +30-2310-994773

**Received:** September 4, 2013  **Revised:** November 2, 2013

**Accepted: January 6, 2014**

**Published online:**

**Abstract**

Ischemic stroke represents a leading cause of mortality and long-term disability worldwide. Given these detrimental effects of acute stroke, several neuroprotective agents have been evaluated in these patients. However, the benefits of the evaluated agents appear to be limited and none is currently recommended for clinical use. On the other hand, prior treatment with agents that are used for the primary and secondary prevention of stroke, including statins and antiplatelets, has been associated with better outcome in patients who experience an acute stroke. In contrast, there are limited data whether prior treatment with antidiabetic agents is beneficial in diabetic patients who suffer a stroke. In this context, the findings of a recent study that showed reduced stroke size following pretreatment with linagliptin, a dipeptidyl peptidase-4 (DDP-4) inhibitor, compared with glimepiride, in both diabetic and non-diabetic mice, appear promising. Despite these preclinical findings suggesting neuroprotective effects of DPP-4 inhibitors in acute stroke, it is still unclear whether these actions will also be observed in humans. Of note, two recent large randomized, placebo-controlled studies did not show any effect of DPP-4 inhibitors on cardiovascular events, including stroke. Several other ongoing trials are evaluating the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality. These studies also provide a major opportunity to assess whether patients treated with this class of antidiabetic agents will suffer from less severe strokes and whether their outcome after stroke will be more favorable.

© 2014 Baishideng Publishing Group Co., Limited. All rights reserved.

**Key words:** Type 2 diabetes mellitus; Stroke; Dipeptidyl peptidase-4 inhibitors; Sulfonylureas; Neuroprotection

**Core tip:** A recent study showed reduced stroke size following pretreatment with linagliptin, a dipeptidyl peptidase-4 (DDP-4) inhibitor, compared with glimepiride, in both diabetic and non-diabetic mice. It remains to be shown whether these neuroprotective actions of DPP-4 inhibitors will also be observed in humans.

Magkou D, Tziomalos K.Antidiabetic treatment and stroke severity and outcome.

**Available from:** URL: http://www.wjgnet.com//

**DOI:** http://dx.doi.org//

**INVITED COMMENTARY ON HOT ARTICLES**

Ischemic stroke represents a leading cause of mortality and long-term disability worldwide[1]. This often disabling and frequently fatal event puts a substantial burden on the family members and medical professionals who care for stroke victims[1].

The increasing prevalence of obesity results in increased incidence of type 2 diabetes mellitus (T2DM) worldwide[2]. T2DM is a major risk factor for cardiovascular events, including stroke[3,4]. In addition, patients with T2DM appear to suffer more severe strokes than subjects without T2DM and have worse outcome than the latter[3,5-7]. The increased incidence of cardiovascular events in patients with T2DM is not only due to hyperglycemia but insulin resistance, low-grade inflammation and activation of the coagulation cascade are also involved[3,8].

Given the high morbidity and mortality rates associated with acute ischemic stroke, several neuroprotective agents have been evaluated in these patients[9]. However, the benefits of the evaluated agents appear to be limited and none is currently recommended for clinical use[9]. On the other hand, prior treatment with agents that are used for the primary and secondary prevention of stroke, including statins and antiplatelets, has been associated with less severe stroke, better functional outcome and reduced mortality in patients who experience an acute stroke[10-13]. In contrast, there are limited data whether prior treatment with antidiabetic agents is beneficial in diabetic patients who suffer a stroke. In an early study, prior treatment with sulfonylureas had no effect on stroke severity or outcome[14]. In contrast, a more recent study suggested that patients who were on sulfonylureas prior to stroke and continued to receive these agents during hospitalization were more likely to have a better neurological and functional outcome at discharge[15]. In another study, diabetic patients who were on sulfonylureas, metformin or insulin prior to stroke had less severe stroke at admission than patients who were not receiving any antidiabetic agent. In contrast, functional outcome and mortality rates at 90 d after stroke were similar in patients who were on glucose-lowering treatment and in those who were not[16]. Stroke severity and outcome did not differ between patients who were on sulfonylureas, metformin or insulin prior to stroke[16]. A small retrospective study also suggested that thiazolidinediones enhance functional recovery in patients with stroke[17] (Table 1).

In this context, the findings of a recent study that compared the effects of pretreatment with glimepiride, a sulfonylurea, and linagliptin, a dipeptidyl peptidase-4 (DDP-4) inhibitor, on the outcome of stroke in diabetic and non-diabetic mice, appear promising[18]. It has been previously reported that administration of sulfonylureas after stroke reduces infarct size and mortality, primarily by preventing cerebral edema[19,20]. In this study, 44 male C57Bl mice were divided into 2 groups. The first group (*n* = 21) was exposed to a high-fat diet for 32 wk, which resulted in substantial weight gain and development of insulin resistance and hyperglycemia[18]. At week 25, this group was assigned to oral administration of 10 mg/kg per body weight (bw) linagliptin daily, 2 mg/kg per body weight glimepiride daily or vehicle[18]. The second group (*n* = 23) was fed a normal diet and was also assigned to linagliptin, glimepiride or vehicle at the same doses with the first group[18]. After 4 wk of treatment, stroke was induced in all mice in both groups by transient occlusion of the middle cerebral artery[18]. Treatment with linagliptin, glimepiride or vehicle was continued for 3 wk following stroke, after which all mice in both groups were sacrificed[18]. The extent of ischemic stroke was assessed with measuring stroke volume and with stereological quantification of surviving neurons in the striatum/cortex[18].

In high-fat diet-fed mice, fed and fasting blood glucose levels decreased in both linagliptin- and glimepiride-treated mice[18]. This reduction was greater in mice treated with glimepiride. In contrast, in normal diet-fed mice, fed and fasting blood glucose levels decreased in glimepiride-treated animals but did not change in linagliptin-treated animals[18]. On the other hand, both high-fat- and normal diet-fed mice that were treated with linagliptin showed an increase in blood glucagon-like peptide-1 (GLP-1) levels due to a significant reduction in DPP-4 activity[18]. In contrast, GLP-1 levels and DPP-4 activity did not change in glimepiride- or vehicle-treated mice regardless of the diet they were fed[18].

Immunohistochemical staining of the cortex/striatum of high-fat diet-fed mice without stroke revealed GLP-1 receptor expression exclusively in the neurons[18]. Cortical pyramidal neurons showed the most pronounced expression of GLP-1 receptors[18].

In high-fat diet-fed mice, treatment with linagliptin resulted in a noticeable, albeit not statistically significant trend towards reduction of stroke volume[18]. In contrast, glimepiride had no effect on stroke volume[18]. Moreover, stereological counting of surviving neurons revealed significantly more (approximately 30%) surviving neurons in linagliptin-treated mice than in either glimepiride- or vehicle-treated animals[18]. In contrast, in normal diet-fed mice, treatment with both linagliptin and glimepiride resulted in a comparable and non-significant trend for reduced stroke volume and was associated with a comparable and significantly higher number of surviving neurons compared with vehicle treatment[18].

Overall, this study[18] suggests that treatment with linagliptin prior stroke increases the number of surviving neurons more than glimepiride in diabetic mice. This neuroprotective effect of linagliptin appears to be glucose-lowering-independent since the reduction in blood glucose levels was smaller during treatment with linagliptin compared with glimepiride. In addition, linagliptin also prevented neuronal death in non-diabetic mice even though it did not affect glucose levels, further supporting a glucose-lowering-independent neuroprotective effect. Similar results have been reported very recently with another DPP-4 inhibitor, alogliptin[21]. Moreover, in humans, even though increased glucose levels at admission are associated with worse outcome in patients with acute ischemic stroke[22-24], correction of hyperglycemia with administration of insulin does not reduce infarct size or neurologic deficit[25-27].

Several alternative mechanisms besides glucose lowering may underpin the beneficial effects of linagliptin in the setting of acute stroke. First, treatment with linagliptin results in increased blood GLP-1 levels and pretreatment with exendin-4, a GLP-1 agonist, was shown to reduce stroke volume and neurological deficit in animal stroke models[28-30]. Antiapoptotic, antiinflammatory and antioxidant actions as well as stimulation of the proliferation of neural stem cells and attenuation of microglial activation appear to contribute to these neuroprotective effects[29-31]. Interestingly, administration of exendin-4 in non-diabetic animals immediately after stroke also reduces stroke volume and improves outcome through similar mechanisms without affecting glucose levels[32]. These effects appear to be GLP-1 receptor-mediated, since they are not observed in GLP-1 receptor knockout (-/-) mice[28]. Moreover, GLP-1 readily crosses the blood-brain barrier[33-35] and GLP-1 receptors are expressed in brain neurons in humans[36-39]. In addition, both ischemia and treatment with exendin-4 up-regulate the expression of GLP-1 receptors in pyramidal neurons[29]. Given the putative neuroprotective effects of GLP-1, this increased expression might represent a defense mechanism against ischemic damage[29].

A second possible pathway through which linagliptin might exert its neuroprotective effects is the increased bioavailability of other bioactive DPP-4 substrates. Indeed, DPP-4 has many other substrates except GLP-1, some of which appear to exert neurotrophic or neuroprotective effects[40,41]. The latter include glucose-dependent insulinotropic polypeptide[42], pituitary adenylate cyclase-activating polypeptide[43] and stromal cell-derived factor 1a[44], which were reported in preclinical models to promote synaptic plasticity, neurogenesis and neuronal differentiation, to inhibit apoptosis and to reduce stroke size.

Another possible explanation of the different effects of linagliptin and glimepiride on stroke volume is that glimepiride exerts detrimental effects rather than that linagliptin is protective. Indeed, several recent studies suggested that patients treated with sulfonylureas have increased cardiovascular morbidity compared with patients treated with metformin[45-47]. Therefore, it would be of interest to compare the effects of prior treatment of DPP-4 inhibitors with prior treatment with metformin in experimental models of stroke or in patients who suffer a stroke.

Despite these promising preclinical findings suggesting neuroprotective effects of DPP-4 inhibitors in acute stroke, it is still unclear whether these actions will also be observed in humans. Interestingly, a recent randomized double-blind study showed that the addition of linagliptin to metformin reduces the risk of non-fatal stroke more than the addition of glimepiride despite comparable decreases in HbA1c[48]. Preliminary data also suggest similar reductions in stroke risk with other DPP-4 inhibitors[49]. However, these studies was neither planned nor powered to assess the effects of DPP-4 inhibitors on cardiovascular events[48,49]. On the other hand, two recent large randomized, placebo-controlled studies did not show any benefit of DPP-4 inhibitors on cardiovascular events, including stroke[50,51]. Several other ongoing trials are evaluating the effects of DPP-4 inhibitors on cardiovascular morbidity and mortality. These studies also provide a major opportunity to assess whether patients treated with this class of antidiabetic agents will suffer from less severe strokes and whether their outcome after stroke will be more favorable.

**REFERENCES**

1. **Donnan GA,** Fisher M, Macleod M, Davis SM. Stroke. *Lancet* 2008; **371:** 1612-1623 [PMID: 18468545 DOI: 10.1016/S0140-6736(08)60694-7]
2. **Nolan CJ,** Damm P, Prentki M. Type 2 diabetes across generations: from pathophysiology to prevention and management. *Lancet* 2011; **378:** 169-181 [PMID: 21705072 DOI: 10.1016/S0140-6736(11)60614-4]
3. **Luitse MJ,** Biessels GJ, Rutten GE, Kappelle LJ. Diabetes, hyperglycaemia, and acute ischaemic stroke. *Lancet Neurol* 2012; **11:** 261-271 [PMID: 22341034 DOI: 10.1016/S1474-4422(12)70005-4]
4. **Emerging Risk Factors Collaboration,** Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, Ingelsson E, Lawlor DA, Selvin E, Stampfer M, Stehouwer CD, Lewington S, Pennells L, Thompson A, Sattar N, White IR, Ray KK, Danesh J. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. *Lancet* 2010; **375:** 2215-2222 [PMID: 20609967 DOI: 10.1016/S0140-6736(10)60484-9]
5. **Hatzitolios AI,** Didangelos TP, Zantidis AT, Tziomalos K, Giannakoulas GA, Karamitsos DT. Diabetes mellitus and cerebrovascular disease: which are the actual data? *J Diabetes Complications* 2009; **23:** 283-296 [PMID: 18358748 DOI: 10.1016/j.jdiacomp.2008.01.004]
6. **Reeves MJ,** Vaidya RS, Fonarow GC, Liang L, Smith EE, Matulonis R, Olson DM, Schwamm LH; Get With The Guidelines Steering Committee and Hospitals. Quality of care and outcomes in patients with diabetes hospitalized with ischemic stroke: findings from Get With the Guidelines-Stroke. *Stroke* 2010; **41:** e409-417 [PMID: 20224058 DOI: 10.1161/STROKEAHA.109.572693]
7. **Megherbi SE,** Milan C, Minier D, Couvreur G, Osseby GV, Tilling K, Di Carlo A, Inzitari D, Wolfe CD, Moreau T, Giroud M; European BIOMED Study of Stroke Care Group. Association between diabetes and stroke subtype on survival and functional outcome 3 months after stroke: data from the European BIOMED Stroke Project. *Stroke* 2003; **34:** 688-694 [PMID: 12624292 DOI: 10.1161/01.STR.0000057975.15221.40]
8. **Haratz S,** Tanne D. Diabetes, hyperglycemia and the management of cerebrovascular disease. *Curr Opin Neurol* 2011; **24:** 81-88 [PMID: 21124220 DOI: 10.1097/WCO.0b013e3283418fed]
9. **Sutherland BA,** Minnerup J, Balami JS, Arba F, Buchan AM, Kleinschnitz C. Neuroprotection for ischaemic stroke: translation from the bench to the bedside. *Int J Stroke* 2012; **7:** 407-418 [PMID: 22394615 DOI: 10.1111/j.1747-4949.2012.00770.x]
10. **Ní Chróinín D,** Asplund K, Åsberg S, Callaly E, Cuadrado-Godia E, Díez-Tejedor E, Di Napoli M, Engelter ST, Furie KL, Giannopoulos S, Gotto AM Jr, Hannon N, Jonsson F, Kapral MK, Martí-Fàbregas J, Martínez-Sánchez P, Milionis HJ, Montaner J, Muscari A, Pikija S, Probstfield J, Rost NS, Thrift AG, Vemmos K, Kelly PJ. Statin therapy and outcome after ischemic stroke: systematic review and meta-analysis of observational studies and randomized trials. *Stroke* 2013; **44:** 448-456 [PMID: 23287777 DOI: 10.1161/STROKEAHA.112.668277]
11. **Athyros VG,** Kakafika AI, Tziomalos K, Papageorgiou AA, Karagiannis A. Statins for the prevention of first or recurrent stroke. *Curr Vasc Pharmacol* 2008; **6:** 124-133 [PMID: 18393914 DOI: 10.2174/157016108783955365]
12. **Tziomalos K**, Giampatzis V, Bouziana SD, Spanou M, Pavlidis A, Papadopoulou M, Boutari C, Magkou D, Savopoulos C, Hatzitolios AI. Effect of prior treatment with different statins on stroke severity and functional outcome at discharge in patients with acute ischemic stroke. *Int J Stroke* 2013; **8:** E49 [PMID: 24024925 DOI: 10.1111/ijs.12116]
13. **Sanossian N,** Saver JL, Rajajee V, Selco SL, Kim D, Razinia T, Ovbiagele B. Premorbid antiplatelet use and ischemic stroke outcomes. *Neurology* 2006; **66:** 319-323 [PMID: 16382033 DOI: 10.1212/01.wnl.0000195889.05792.f1]
14. **Weih M,** Amberger N, Wegener S, Dirnagl U, Reuter T, Einhäupl K. Sulfonylurea drugs do not influence initial stroke severity and in-hospital outcome in stroke patients with diabetes. *Stroke* 2001; **32:** 2029-2032 [PMID: 11546892]
15. **Kunte H,** Schmidt S, Eliasziw M, del Zoppo GJ, Simard JM, Masuhr F, Weih M, Dirnagl U. Sulfonylureas improve outcome in patients with type 2 diabetes and acute ischemic stroke. *Stroke* 2007; **38:** 2526-2530 [PMID: 17673715 DOI: 10.1161/STROKEAHA.107.482216]
16. **Favilla CG,** Mullen MT, Ali M, Higgins P, Kasner SE; Virtual International Stroke Trials Archive (VISTA) Collaboration. Sulfonylurea use before stroke does not influence outcome. *Stroke* 2011; **42:** 710-715 [PMID: 21330623 DOI: 10.1161/STROKEAHA.110.599274]
17. **Lee J,** Reding M. Effects of thiazolidinediones on stroke recovery: a case-matched controlled study. *Neurochem Res* 2007; **32:** 635-638 [PMID: 16960755 DOI: 10.1007/s11064-006-9138-3]
18. **Darsalia V,** Ortsäter H, Olverling A, Darlöf E, Wolbert P, Nyström T, Klein T, Sjöholm Å, Patrone C. The DPP-4 inhibitor linagliptin counteracts stroke in the normal and diabetic mouse brain: a comparison with glimepiride. *Diabetes* 2013; **62:** 1289-1296 [PMID: 23209191 DOI: 10.2337/db12-0988]
19. **Simard JM,** Chen M, Tarasov KV, Bhatta S, Ivanova S, Melnitchenko L, Tsymbalyuk N, West GA, Gerzanich V. Newly expressed SUR1-regulated NC(Ca-ATP) channel mediates cerebral edema after ischemic stroke. *Nat Med* 2006; **12:** 433-440 [PMID: 16550187 DOI: 10.1038/nm1390]
20. **Simard JM,** Yurovsky V, Tsymbalyuk N, Melnichenko L, Ivanova S, Gerzanich V. Protective effect of delayed treatment with low-dose glibenclamide in three models of ischemic stroke. *Stroke* 2009; **40:** 604-609 [PMID: 19023097 DOI: 10.1161/STROKEAHA.108.522409]
21. **Yang D,** Nakajo Y, Iihara K, Kataoka H, Yanamoto H. Alogliptin, a dipeptidylpeptidase-4 inhibitor, for patients with diabetes mellitus type 2, induces tolerance to focal cerebral ischemia in non-diabetic, normal mice. *Brain Res* 2013; **1517:** 104-113 [PMID: 23602966 DOI: 10.1016/j.brainres.2013.04.015]
22. **Capes SE,** Hunt D, Malmberg K, Pathak P, Gerstein HC. Stress hyperglycemia and prognosis of stroke in nondiabetic and diabetic patients: a systematic overview. *Stroke* 2001; **32:** 2426-2432 [PMID: 11588337 DOI: 10.1161/hs1001.096194]
23. **Bruno A,** Levine SR, Frankel MR, Brott TG, Lin Y, Tilley BC, Lyden PD, Broderick JP, Kwiatkowski TG, Fineberg SE; NINDS rt-PA Stroke Study Group. Admission glucose level and clinical outcomes in the NINDS rt-PA Stroke Trial. *Neurology* 2002; **59:** 669-674 [PMID: 12221155 DOI: 10.1212/WNL.59.5.669]
24. **Stead LG,** Gilmore RM, Bellolio MF, Mishra S, Bhagra A, Vaidyanathan L, Decker WW, Brown RD Jr. Hyperglycemia as an independent predictor of worse outcome in non-diabetic patients presenting with acute ischemic stroke. *Neurocrit Care* 2009; **10:** 181-186 [PMID: 18357419 DOI: 10.1007/s12028-008-9080-0]
25. **Gray CS,** Hildreth AJ, Sandercock PA, O'Connell JE, Johnston DE, Cartlidge NE, Bamford JM, James OF, Alberti KG; GIST Trialists Collaboration. Glucose-potassium-insulin infusions in the management of post-stroke hyperglycaemia: the UK Glucose Insulin in Stroke Trial (GIST-UK). *Lancet Neurol* 2007; **6:** 397-406 [PMID: 17434094 DOI: 10.1016/S1474-4422(07)70080-7]
26. **McCormick M,** Hadley D, McLean JR, Macfarlane JA, Condon B, Muir KW. Randomized, controlled trial of insulin for acute poststroke hyperglycemia. *Ann Neurol* 2010; **67:** 570-578 [PMID: 20437554 DOI: 10.1002/ana.21983]
27. **Bellolio MF,** Gilmore RM, Stead LG. Insulin for glycaemic control in acute ischaemic stroke. *Cochrane Database Syst Rev* 2011; **9:** CD005346 [PMID: 21901697 DOI: 10.1002/14651858.CD005346.pub3]
28. **Li Y,** Perry T, Kindy MS, Harvey BK, Tweedie D, Holloway HW, Powers K, Shen H, Egan JM, Sambamurti K, Brossi A, Lahiri DK, Mattson MP, Hoffer BJ, Wang Y, Greig NH. GLP-1 receptor stimulation preserves primary cortical and dopaminergic neurons in cellular and rodent models of stroke and Parkinsonism. *Proc Natl Acad Sci U S A* 2009; **106:** 1285-1290 [PMID: 19164583 DOI: 10.1073/pnas.0806720106]
29. **Lee CH,** Yan B, Yoo KY, Choi JH, Kwon SH, Her S, Sohn Y, Hwang IK, Cho JH, Kim YM, Won MH. Ischemia-induced changes in glucagon-like peptide-1 receptor and neuroprotective effect of its agonist, exendin-4, in experimental transient cerebral ischemia. *J Neurosci Res* 2011; **89:** 1103-1113 [PMID: 21472764 DOI: 10.1002/jnr.22596]
30. **Briyal S,** Gulati K, Gulati A. Repeated administration of exendin-4 reduces focal cerebral ischemia-induced infarction in rats. *Brain Res* 2012; **1427:** 23-34 [PMID: 22055454 DOI: 10.1016/j.brainres.2011.10.026]
31. **Darsalia V,** Mansouri S, Ortsäter H, Olverling A, Nozadze N, Kappe C, Iverfeldt K, Tracy LM, Grankvist N, Sjöholm Å, Patrone C. Glucagon-like peptide-1 receptor activation reduces ischaemic brain damage following stroke in Type 2 diabetic rats. *Clin Sci (Lond)* 2012; **122**: 473-483 [PMID: 22150224 DOI: 10.1042/CS20110374]
32. **Teramoto S,** Miyamoto N, Yatomi K, Tanaka Y, Oishi H, Arai H, Hattori N, Urabe T. Exendin-4, a glucagon-like peptide-1 receptor agonist, provides neuroprotection in mice transient focal cerebral ischemia. *J Cereb Blood Flow Metab* 2011; **31:** 1696-1705 [PMID: 21487412 DOI: 10.1038/jcbfm.2011.51]
33. **Kastin AJ,** Akerstrom V, Pan W. Interactions of glucagon-like peptide-1 (GLP-1) with the blood-brain barrier. *J Mol Neurosci* 2002; **18:** 7-14 [PMID: 11931352 DOI: 10.1385/JMN:18:1-2:07]
34. **Kastin AJ,** Akerstrom V. Entry of exendin-4 into brain is rapid but may be limited at high doses. *Int J Obes Relat Metab Disord* 2003; **27:** 313-318 [PMID: 12629557 DOI: 10.1038/sj.ijo.0802206]
35. **Banks WA,** During MJ, Niehoff ML. Brain uptake of the glucagon-like peptide-1 antagonist exendin (9-39) after intranasal administration. *J Pharmacol Exp Ther* 2004; **309:** 469-475 [PMID: 14724226 DOI: 10.1124/jpet.103.063222]
36. **Wei Y,** Mojsov S. Tissue-specific expression of the human receptor for glucagon-like peptide-I: brain, heart and pancreatic forms have the same deduced amino acid sequences. *FEBS Lett* 1995; **358:** 219-224 [PMID: 7843404 DOI: 10.1016/0014-5793(94)01430-9]
37. **Satoh F,** Beak SA, Small CJ, Falzon M, Ghatei MA, Bloom SR, Smith DM. Characterization of human and rat glucagon-like peptide-1 receptors in the neurointermediate lobe: lack of coupling to either stimulation or inhibition of adenylyl cyclase. *Endocrinology* 2000; **141:** 1301-1309 [PMID: 10746632 DOI: 10.1210/en.141.4.1301]
38. **Alvarez E,** Martínez MD, Roncero I, Chowen JA, García-Cuartero B, Gispert JD, Sanz C, Vázquez P, Maldonado A, de Cáceres J, Desco M, Pozo MA, Blázquez E. The expression of GLP-1 receptor mRNA and protein allows the effect of GLP-1 on glucose metabolism in the human hypothalamus and brainstem. *J Neurochem* 2005; **92:** 798-806 [PMID: 15686481 DOI: 10.1111/j.1471-4159.2004.02914.x]
39. **Hamilton A,** Hölscher C. Receptors for the incretin glucagon-like peptide-1 are expressed on neurons in the central nervous system. *Neuroreport* 2009; **20:** 1161-1166 [PMID: 19617854 DOI: 10.1097/WNR.0b013e32832fbf14]
40. **Ahrén B,** Hughes TE. Inhibition of dipeptidyl peptidase-4 augments insulin secretion in response to exogenously administered glucagon-like peptide-1, glucose-dependent insulinotropic polypeptide, pituitary adenylate cyclase-activating polypeptide, and gastrin-releasing peptide in mice. *Endocrinology* 2005; **146:** 2055-2059 [PMID: 15604213 DOI: 10.1210/en.2004-1174]
41. **Mentlein R**. Dipeptidyl-peptidase IV (CD26)--role in the inactivation of regulatory peptides. *Regul Pept* 1999; **85:** 9-24 [PMID: 10588446 DOI: 10.1016/S0167-0115(99)00089-0]
42. **Figueiredo CP,** Pamplona FA, Mazzuco TL, Aguiar AS Jr, Walz R, Prediger RD. Role of the glucose-dependent insulinotropic polypeptide and its receptor in the central nervous system: therapeutic potential in neurological diseases. *Behav Pharmacol* 2010; **21:** 394-408 [PMID: 20574409 DOI: 10.1097/FBP.0b013e32833c8544]
43. **Reglodi D,** Somogyvari-Vigh A, Vigh S, Kozicz T, Arimura A. Delayed systemic administration of PACAP38 is neuroprotective in transient middle cerebral artery occlusion in the rat. *Stroke* 2000; **31:** 1411-1417 [PMID: 10835464 DOI: 10.1161/01.STR.31.6.1411]
44. **Yoo J,** Seo JJ, Eom JH, Hwang DY. Effects of stromal cell-derived factor 1α delivered at different phases of transient focal ischemia in rats. *Neuroscience* 2012; **209:** 171-186 [PMID: 22402345 DOI: 10.1016/j.neuroscience.2012.02.031]
45. **Roumie CL,** Hung AM, Greevy RA, Grijalva CG, Liu X, Murff HJ, Elasy TA, Griffin MR. Comparative effectiveness of sulfonylurea and metformin monotherapy on cardiovascular events in type 2 diabetes mellitus: a cohort study. *Ann Intern Med* 2012; **157:** 601-610 [PMID: 23128859 DOI: 10.7326/0003-4819-157-9-201211060-00003]
46. **Currie CJ,** Poole CD, Evans M, Peters JR, Morgan CL. Mortality and other important diabetes-related outcomes with insulin vs other antihyperglycemic therapies in type 2 diabetes. *J Clin Endocrinol Metab* 2013; **98:** 668-677 [PMID: 23372169 DOI: 10.1210/jc.2012-3042]
47. **Phung OJ,** Schwartzman E, Allen RW, Engel SS, Rajpathak SN. Sulphonylureas and risk of cardiovascular disease: systematic review and meta-analysis. *Diabet Med* 2013; **30:** 1160-1171 [PMID: 23663156 DOI: 10.1111/dme.12232]
48. **Gallwitz B,** Rosenstock J, Rauch T, Bhattacharya S, Patel S, von Eynatten M, Dugi KA, Woerle HJ. 2-year efficacy and safety of linagliptin compared with glimepiride in patients with type 2 diabetes inadequately controlled on metformin: a randomised, double-blind, non-inferiority trial. *Lancet* 2012; **380:** 475-483 [PMID: 22748821 DOI: 10.1016/S0140-6736(12)60691-6]
49. **Frederich R,** Alexander JH, Fiedorek FT, Donovan M, Berglind N, Harris S, Chen R, Wolf R, Mahaffey KW. A systematic assessment of cardiovascular outcomes in the saxagliptin drug development program for type 2 diabetes. *Postgrad Med* 2010; **122:** 16-27 [PMID: 20463410 DOI: 10.3810/pgm.2010.05.2138]
50. **Scirica BM,** Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, Ohman P, Frederich R, Wiviott SD, Hoffman EB, Cavender MA, Udell JA, Desai NR, Mozenson O, McGuire DK, Ray KK, Leiter LA, Raz I; the SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus. *N Engl J Med* 2013; **369:** 1317-1326 [PMID: 23992601 DOI: 10.1056/NEJMoa1307684]
51. **White WB,** Cannon CP, Heller SR, Nissen SE, Bergenstal RM, Bakris GL, Perez AT, Fleck PR, Mehta CR, Kupfer S, Wilson C, Cushman WC, Zannad F; the EXAMINE Investigators. Alogliptin after Acute Coronary Syndrome in Patients with Type 2 Diabetes. *N Engl J Med* 2013; **369:** 1327-1335 [PMID: 23992602 DOI: 10.1056/NEJMoa1305889]

**P- Reviewers:** Padwal R, Piperi C, Zdravkovic M  **S- Editor:** Cui XM

**L- Editor: E- Editor:**

**Table 1** **Major studies that evaluated the effects of antidiabetic agents on stroke severity and outcome**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Ref.** | **Design** | ***n*** | **Agent** | **Results** |
| 14 | Retrospective | 146 | Sulfonylureas | No effect on stroke severity or outcome |
| 15 | Retrospective | 61 | Sulfonylureas | Better neurological and functional outcome at discharge in patients who were on sulfonylureas prior to stroke |
| 16 | Prospective | 1050 | Sulfonylureas, metformin, insulin | Less severe stroke at admission in patients who were on sulfonylureas, metformin or insulin prior to stroke than in patients who were not receiving any antidiabetic agent but no difference in functional outcome and mortality rates at 90 d between the 2 groups  Similar stroke severity and outcome between patients treated with different antidiabetic agents prior to stroke (sulfonylureas, metformin and insulin) |
| 17 | Case-control | 60 | Thiazolidinediones | Enhanced functional recovery in patients treated with thiazolidinediones |