WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 9, Issue 1, 745-763. Review Article ISSN 2277– 7105

TARGETED PROTEINS FOR RECENT AND EMERGING DIABETES MELLITUS RESEARCH

Kuldeep Singh Patel*[1,4], Jagdish Chandra Rathi[2], Vivek Jain[3] and Neeripama Dhamin[4]

[1]NRI Institute of Research and Technology, Sajjan Singh Nagar Raisen Road Bhopal, M.P India 462022.

[2]NRI Institute of Pharmaceutical Sciences, 3, Sajjan Singh Nagar Bhopal, M.P India 462022.

[3]NRI Institute of Pharmacy, Sajjan Singh Nagar Bhopal, M.P India 462022.

[4]Amity Institute of Pharmacy, Amity University, Noida, Uttar Pradesh, India 201307.

Article Received on
31 Oct. 2019,
Revised on 21 Nov. 2019,
Accepted on 11 Dec. 2019
DOI: 10.20959/wjpr20201-16464

***Corresponding Author**
Kuldeep Singh Patel
NRI Institute of Research and Technology, Sajjan Singh Nagar Raisen Road Bhopal, M.P India 462022.

ABSTRACT

Diabetes mellitus (DM) is a major degenerative disease in the world today. Several epidemiological and clinical studies indicate a direct relationship between hyperglycemia and long-term complications such as retinopathy, nephropathy, neuropathy and angiopathy, etc. India has today become the diabetic capital of the world with over 20 million diabetics and this number is set to increase to 57 million by 2025. It is ranked seventh among the leading causes of death and is considered third when its fatal complications are taken into account. DM is a multifactorial disease which is characterized by hyperglycemia, lipoprotein abnormalities, raised basal metabolic rate, defect in reactive oxygen species scavenging enzymes and high oxidative stress-induced damage to pancreatic beta cells. Several drugs are presently available to reduce hyperglycemia in diabetes mellitus. These drugs have side effects and thus searching for a new class of compounds is essential to overcome this problems. Nevertheless, there is continuous search for alternative drugs; management of diabetes without any side effects is still a challenge to the medicinal chemist. Therefore, it is prudent to look for options in novel drugs for diabetes. In this review article, we will review the role of future new chemicals entities able to target the metabolic disorder. Some of these new anti-diabetic treatment strategies may in the future not only control symptoms and modify the natural course of diabetes, but also potentially prevent or cure the disease.

KEYWORDS: Diabetes Mellitus, Metabolic Disorder, Antidiabetics, DPP-IV Inhibitors.

INTRODUCTION

The World Health Organization (WHO) estimates that more than 180 million people worldwide have diabetes. This number is likely to more than double by 2030. Both type 1 and type 2 DM are increasing in frequency. The reason for the increase of type 1 DM is not known. The genetic basis for type 2 DM cannot change in such a short time; thus other contributing factors, including increasing age, obesity, sedentary lifestyle, and low birth weight, must account for this dramatic increase. In addition, type 2 DM is being diagnosed with remarkable frequency in preadolescents and adolescents. Up to 45% of newly diagnosed children and adolescents have type 2 Diabetes Mellitus. The incidence of each type of diabetes varies widely throughout the world. In the United States, about 5% to 10% of all diabetic patients have type 1 DM, with an incidence of 18 per 100,000 inhabitants per year. A similar incidence is found in the United Kingdom. The incidence of type 1 DM in Europe varies with latitude. The highest rates occur in northern Europe (Finland, 43 per 100,000) and the lowest in the south (France and Italy, 8 per 100,000). The one exception to this rule is the small island of Sardinia, close to Italy, which has an incidence of 30 per 100,000. However, even the relatively low incidence rates of type 1 DM in southern Europe are far higher than the rates in Japan.

NEWER APPROACHES

Current Pharmacotherapy

Once a diagnosis of diabetes or metabolic syndrome has been established, then efforts to relieve the symptoms of this disease begin. The initial steps include various life style changes to provide weight control such as dietary modification to include caloric budgeting and reduced intake of high fat and high glycemic index foods, exercise to include aerobic and resistance training to increase metabolic rate and muscle mass (i.e., elevated glucose disposition from blood stream). Failing correction of the signs of metabolic syndrome or diabetes with lifestyle modifications, the patient is placed on oral anti-diabetic pharmacotherapy. Typically monotherapy is the first step, however the trend is to monitor disease progression carefully, provide clear goal-oriented endpoints such as HbA1c below 7.0%, and advance to combination therapy earlier if goals not achieved. Historically injected insulin is reserved for patients who fail to adequately respond to combination therapy or those with safety concerns such as pregnancy, or severe renal, or liver impairment. There is some

movement toward earlier insulin use and insulin in combination with oral agents to try to slow disease progression. Although insulin is the workhorse in late stage disease and a variety of insulin products are available and in development. Oral agents can be classified occurring to their mode of action. Currently there are five mechanistic classes of anti-diabetic agents to include:

1. Carbohydrate modulators which delay intestinal absorption of monosaccharides (i.e., α-glucosidase inhibitors).
2. Insulin secretagogues which increase the exocytosis of insulin from β-cells (sulfonylureas and other Potassium channel stimulators such as repaglinide, nateglinide, etc.).
3. Agents which have direct insulin sensitizing effects on peripheral insulin responsive tissues (biguanides such as metformin; peroxisome proliferator-activated receptor gamma (PPARγ) full agonists such as rosiglitazone and pioglitazone).
4. Incretin potentiators (exenatide is an incretin analog and sitagliptin is an inhibitor of incretin degradation).
5. Amylin analog (pramlintide).

As physicians assess their patients with regard to their glycemic control, they attempt to match their needs to the unique pharmacodynamic and side effect profiles of the agents mentioned above and described briefly below. How the known drugs work (cellular targets and observed effects) and their appropriate use (indication, contraindication, side effects) is outlined below.[27]

A. Carbohydrate Modulators (α -Glucosidase Inhibitors)

Alpha-Glucosidase inhibitors such as acarbose competitively inhibit the activity of α-glucosidase enzymes in the brush border of enterocytes lining the intestinal villi. This inhibits the cleaving of di and oligosaccharides to monosaccharides such as glucose prior to absorption. This delays the absorption of glucose and alters the release of glucose-dependent intestinal hormones. These agents are indicated as monotherapy in patients inadequately controlled on non-pharmacological measures. They can be particularly useful in patients who experience marked post-prandial hyperglycemia but otherwise have well controlled basal glucose concentrations.

The typical decrease in HbA1c levels is 0.5–1.0%, however to have this effect the diet must be rich in complex carbohydrates and high doses of drug must be tolerated. The most common side effects are gastrointestinal in nature and include abdominal discomfort and

diarrhoea. α-Glucosidase inhibitors were first used in the early 1990s and owing to high cost and limited efficacy, the use of this class remains low.

B. Insulin Secretagogues (Sulfonylureas and Other K Directed Agents Such as Repaglinide, Nateglinide, etc.)

Sulfonylureas are a class of agents used since the 1960s that bind the sulfonylurea receptor (SUR-1) in β-cells. SUR-1 binding closes K_{ATP} channels lowering the depolarization threshold of the membrane. Depolarization opens Ca^{++} channels increasing intracellular Ca^{++} levels and facilitates insulin release. A second generation of more potent sulfonylureas has been available since the 1990s. These agents are popularly used as first-line therapy in patients that have not achieved adequate glycemic control using non-pharmacological measures. Typically sulfonylureas decrease HbA1c by 1–2%; however responses are variable and are dependent on functional β-cells. Secondary sulfonylurea urea failure (i.e., deterioration of glycemic control over time) along with the most common adverse effect, frequent hypoglycaemia some times requires that they be used in combination therapy with metformin or PPARγ agonists. The inexpensive cost, the potent glycemic control, and utility in combination therapy make sulfonylureas use very common despite the observation of weight gain in some patients.

Another class that is highly related in terms of mechanism of action is the rapid-acting prandial insulin releasers. Examples include meglitinide, repaglinide, and nateglinide, which bind to an alternative binding site on SUR-1 and have similar effects. These, like the sulfonylureas are very effective at suppressing post-prandial hepatic glucose production and are used appropriately in patients with poor post-prandial glucose control.

C. Insulin Sensitizers (Biguanides and Thiazolidinediones)

Insulin sensitizers have direct pleiotropic effects on insulin responsive tissues, generally enhancing insulin sensitivity in these tissues. Insulin sensitizers improve insulin action at the target tissue level so the requirement for functional β-cells is not as stringent. Nonetheless, these agents can be helpful in early metabolic syndrome patients or insulin dependent diabetics. Biguanides as a class were derived from traditional European herbal therapies of the 1920s involving Galega officinalis which was rich in glucose-lowering guanidine derivatives.

Several biguanides were reported in the 1950s to include metformin, phenformin, and buformin. The only remaining biguanide in the US is metformin (approved in 1995). Although the molecular mechanisms of metformin are not completely understood, evidence suggests that AMP-activated protein kinase (AMPK; an emerging target reviewed infra) is an indirect target for metformin. Unlike sulfonylureas, metformin does not stimulate insulin release and lowers blood glucose without causing overt hypoglycaemia (i.e., anti-hyperglycaemic vs. hypoglycaemic). Metformin exerts insulin sensitizing influences on multiple tissues to include liver (decreased HGP via suppressed GNG and glycogenolysis), fat (decreased FFA production via increased glucose uptake and oxidation), muscle (increased insulin mediated glucose disposal via increased uptake and glycogenesis, decreased fatty acid oxidation), and intestine (increased anaerobic glucose metabolism). Through these pleiotropic effects, metformin counters IR and reduces gluco- and lipotoxicity. Metformin is first-line therapy of choice for overweight and obese patients and is commonly used as monotherapy or in combination.

However, there are some contraindications to its use to include impaired renal function (annual serum creatinine testing is advised), liver disease, or history of metabolic acidosis.

Typically, metformin decreases HbA1c by 1–2% however, this is somewhat dependent upon some degree of endogenous β-cell function (less so than sulfonylureas). Clinical benefits also include lack of hypoglycaemic liability, reduced basal insulin secretion, stabilized to decreased body weight, and improvements in low- and high density lipoproteins (LDL; HDL) levels. Lastly certain vasoprotective properties are alleged based on increased fibrinolysis and reduced anti-thrombotic factor plasminogen activator inhibitor-1(PAI-1).

The most common adverse effects are abdominal discomfort and diarrhoea in approximately 10%. Due to potent anti-hyperglycaemic effects, other ancillary clinical benefits, utility in combination therapy, and inexpensive cost, metformin is among the most commonly prescribed oral agents.

D. Peroxisome Proliferator-Activated Receptor Gamma (PPARγ) Agonists (Thiazolidinediones)

TZD improve whole body insulin sensitivity via the activation of PPARγ in a variety of different tissues. The nuclear receptor PPARγ is activated by endogenous lipids and prostaglandins, and modulates the transcription of a broad program of genes. The first TZD,

troglitazone was approved in 1997 but was pulled from the market due to hepatotoxicity. Currently rosiglitazone and pioglitazone are the only TZD available in the US. TZD have a variety of metabolic effects in adipose tissue (increased glucose uptake, FA uptake, lipogenesis, and pre-adipocyte differentiation), muscle (increased glucose uptake, glycolysis, and glycogenesis), and liver (decreased GNG, glycogenolysis; increased lipogenesis and glucose uptake). TZD, like metformin, are anti-hyperglycaemic agents which additionally reduce insulin concentrations and lower TG in the blood. However unlike metformin, TZD tend to promote fat synthesis and increased body weight. TZD are available for non-obese and obese patients failing non-pharmacological therapy and can be used as mono- or combination therapy. Side effects of TZD therapy have garnered significant attention in the lay press and include fluid retention which worsens cardiac failure and predisposes to myocardial infarction, and weight gain of 1–4 kg. TZD also induced anaemia, and are contraindicated in active liver disease, heart failure, insulin-dependence (in Europe; rationale is edema is worse), and pregnancy. The anti- hyperglycaemic effects require 2–3 months to reach maximum efficacy which can reduce HbA1c by 0.5–1.5%, particularly if some β-cell function is intact. Also TZD might reduce the risk of atherosclerotic cardiovascular disease due to low-grade reductions in inflammation and reduced PAI-1 expression. Despite widely publicized adverse effects and moderate cost, TZD is still widely used. Alternative agents targeting different PPAR isoforms remain active areas of research in pharmaceutical company pipelines.

E. Incretin Potentiators (Exenatide and Sitagliptin)

Incretins are gut-derived peptide hormones that are rapidly secreted in response to meal initiation. The two main incretins in humans, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) stimulate pancreatic β-cells within 10 min of a meal to secrete insulin. This effect accounts for 50–60% of the total post-prandial insulin response in healthy individuals. The incretin effect is specific to oral ingestion (i.e., not observed with glucose given intravenously) and can be defined as an enhanced insulin response to oral glucose loads when compared to intravenous glucose loads. Incretins are also believed to stimulate β-cell growth and prevent b -cell apoptosis, suggesting that therapeutic agents based on this target may have the ability to alter the natural history of diabetes (i.e., progressive β-cell functional decline). Unfortunately, the response to GIP is blunted in DM-II making the GIP-directed agent's poor pharmacotherapy. However, FDA has approved a couple of incretin directed agents that potentiate GLP-1 receptor (GLP-1R).

F. DPP-IV Inhibitors (Sitagliptin)

The incretin effect is limited by the action of the serine protease DPP-IV which rapidly cleaves GLP-1 and GIP. This hypothesis was supported by the observation in DPP-IV knockout mice in which GIP and GLP-1 levels were increased and demonstrated enhanced insulin secretion after oral glucose challenge. A theoretical advantage of DPP-IV inhibitors is that they would also potentiate the effects of GIP and other incretins. Sitagliptin was the first DPP-IV inhibitor approved in 2006. Sitagliptin significantly lowers blood glucose and HbA when used as monotherapy but these effects were not as potent as metformin. However, addition of sitagliptin to metformin or TZD produced significant improvements in HbA and resulted in a greater portion of patients reaching HbA1c < 7%. The most common side effects of sitagliptin are gastrointestinal complaints and nasopharyngitis. Sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes mellitus as monotherapy, or in combination with TZD or metformin.

G. GLP-1 Receptor (GLP-1R) Agonist (Exenatide)

Exenatide is a polypeptide that was originally isolated from the venom of gila monsters and exhibits 53% identitywithGLP-1. However it is 10 to100 fold more potent than endogenous GLP-1owing to its resistance to degradation by dipeptidyl peptidase-IV (DPP-IV) which typically completely degrades incretins within a few minutes of their secretion. Exenatide is administered via subcutaneous injection twice a day and produces significant reduction in HbA, FPG, and post- prandial glucose levels. Exenatide achieved HbA1c levels < 7% (average decline of 0.8%) in 46% of patients that failed metformin with a mean weight loss of 2.8kg. The most common side effect is nausea and occasion hypoglycemia. Exenatide is indicated as adjunctive therapy to improve glycemic control in DM-II patients who are taking metformin, a sulfonylurea, a TZD, or a combination thereof, but have not achieved adequate glycemic control.

An advantage of exenatide or sitagliptin is reduction in HbA1c without weight gain commonly seen with insulin, sulfonylureas, and TZD. Also the prospect of preservation of b-cells function suggests that they may alter the natural history of diabetes, however this long-term effect has not yet been observed clinically. Moreover, these agents provide another option for clinicians to improve glycemic control (including for patients failing combination therapy) and thus forestall progression to insulin dependency.

H. Amylin Analog (Pramlintide)

Amylin, discovered in 1987, is a peptide hormone co-secreted with insulin from the pancreatic b-cells in response to glucose absorption. Amylin binds to a G-protein coupled receptor (GPCR) that suppresses glucagon secretion, slows gastric emptying time, and reduces food intake (i.e., satiating effect). Post-prandial blood glucose is significantly lowered by the cumulative effects of these three activities of amylin. Despite the diversity of effects, amylin acts as a neuroendocrine hormone exerting its metabolic effects centrally. Pramlintide is an equipotent analog (amino acids A25, S28, and S29 are changed to avoid aggregation problems with amylin) that was approved in 2005 for type 1 and 2 diabetics who have not achieved glucose control as an adjunctive to meal time insulin (with or without sulfonylurea and/or metformin). It is administered subcutaneously before each meal of > 250 calories (skip dose if meal skipped) at a location >2 inches from the insulin injection site. The most common side effects are hypoglycemia, nausea and vomiting (particularly with over eating, and anorexia), and the only contraindications are allergy and confirmed diagnosis of gastroparesis. In DM-II patients, pramlintide was associated with 0.5% HbA1c reduction and 0.5– 1.4 Kg body weight reduction. Because pramlintide is an injectable that must be given with each meal, its use is limited to patients who tolerate multiple injections in addition to insulin, and may be suggested for patients whose HbA1c are < 8% but still need further reduction in post-prandial glucose levels and/or have a body mass index of >35 kg/m (i.e., morbidly obese). Also self-monitoring of blood glucose (SMBG) within 1–4 hr after eating is imperative for determining the appropriate preprandial insulin bolus doses and adjusting their timing.

I. Inadequacy of Current Pharmacotherapy

Despite the large number of agents and the mechanistic diversity that they embody, 63% of DM-II patients fail to reach goal HbA1c levels of < 7% as advised by the American Diabetes Association, and are thus at high risk of developing complications. Moreover, almost invariably patients progress through the stages of declining pancreatic function. Consequently there is still an urgent need for novel anti-diabetic agents that affect diverse biological targets.

Current Concepts of Pparγ Signaling in Diabetes Mellitus

The peroxisome is a sub cellular organelle whose functions extend well beyond the removal of molecular oxygen and later breakdown of hydrogen peroxide, to include glycerolipid synthesis, cholesterol biosynthesis and breakdown, and fatty-acid oxidation. The fact that

proliferation of peroxisomes induced in rodents is associated with a multitude of biochemical changes has been for a long time contrasted with the uncertainty about the underlying mechanisms of peroxisome proliferation. Essentially, the discovery of the first peroxisome proliferator-activated receptor (PPAR) by Issemann and Green was the key to the present understanding of peroxisome proliferation and its growing medical significance.

PPARγ and Insulin Resistance/Type 2 diabetes

A more pleiotropic role has been recently assigned to PPARγ as it influences multiple fundamental pathways in the cell with wide-ranging biomedical implications. In particular, studies looking into the molecular basis of insulin resistance have focused on the PPARγ, as they increase our understanding of the pathophysiology of Type 2 diabetes and also lead to the development of newer anti-diabetic agents. Type 2 diabetes is a major medical problem, the incidence of which is escalating rapidly in developing countries; with India harbouring the largest ever number of diabetics in the world. Insulin resistance is one of the principal defects underlying the development of Type 2 diabetes and Indians are considered to be more insulin-resistant. Additionally, the prevalence of micro and macrovascular complications associated with diabetes is also increasing in epidemic proportions. There is a general consensus that targeting insulin resistance early in the course of the disease may help achieve optimal glycemic control, halt disease progression, and probably even prevent the diabetic complications. This view has been strengthened by the recent trials of thiazolidinedione group of drugs that treat diabetes by increasing the sensitivity of insulin's action, primarily acting through PPARγ signalling.

Cellular abundance of PPARγ

Although PPARγ expression is detected in the nucleus of many cells, only adipose tissue, large intestine and haematopoietic cells express the highest levels of PPARγ mRNA and protein. Human muscle tissue expresses only trace amounts of PPARγ under basal conditions. However, PPARγ mRNA has been identified in skeletal muscle and is found to be increased in obese subjects with insulin resistance. The expression of PPARγ mRNA or protein or both in adipose tissue changes under the influence of a number of metabolic and hormonal variables. While short-term changes in food intake do not affect the expression of human PPARγ, hypocaloric diets for a longer period result in its down regulation. In rodents, PPARγ is down regulated by fasting and insulin-dependent diabetes mellitus whereas its expression is induced by a high-fat diet. Interestingly, PPARγ expression is highly enriched in

subcutaneous fat in normal weight subjects and its higher expression culminates in visceral adipose tissue in obese subjects. Additional experiments also point out its regulation by insulin, tumour necrosis factor *a* (TNF*a*) and glucocorticoids. Moreover, the tissue specific expression of PPARγ in endothelial and vascular smooth muscle cells suggests their causal and additional influence on vascular tone and elevated blood pressure.

While PPARγ seems to have its primary effects on adipose tissue, it is a paradox how PPARγ agonists improve insulin sensitivity in muscle, where glucose uptake maximally occurs. It is important to note that on a whole-body level, adipose tissue is indispensable for glucose homeostasis, as demonstrated by the link between lipoatrophy and insulin resistance, suggesting that the adipogenic activity of PPARγ contributes to insulin sensitization. In a nutshell, short-term storage of excess energy, secondary to PPARγ activity, ameliorates insulin sensitivity. Nevertheless, the low abundance of PPARγ mRNA and protein in muscle tissue poses a question. Is PPARγ essential for the normal action of insulin and uptake of glucose? According to Auwerx, minute quantities of PPARγ in muscle might, however, be sufficient or alternatively might be induced during treatment with thiazolidinedione, leading to an eventual direct PPARγ mediated response of the muscle to these insulin sensitizers.

CONCLUSION

Newer approaches mentioned in this article have been directed at improving currently available anti-diabetic drugs and finding the new compounds. The role of future new chemical entities will be to target the metabolic disorder through multi-facet mechanisms. Some of these new anti-diabetic treatment strategies may in the future not only control symptoms and modify the natural course of diabetes, but also potentially prevent or cure the disease.

ACKNOWLEDGEMENT

The authors are thankful and acknowledge the support given by D. Subodh Singh, Chairman NRI Institute of Research & Technology Bhopal, M.P India for providing Facilities of this study.

REFERENCES

1. Abbas T, Faivre E, Holscher C. Impairment of synaptic plasticity and memory formation in GLP-1 receptor KO mice: interaction between type 2 diabetes and Alzheimer's disease. Behav Brain Res., 2009; 205: 265-71.

2. Adler BL, Yarchoan M, Hwang HM, Louneva N, Blair JA, Palm R, et al. Casadesus G Neuroprotective effects of the amylin analogue pramlintide on Alzheimer's disease pathogenesis and cognition. Neurobiol Aging, 2014; 35: 793-801.
3. Aisen PS. The potential of anti-inflammatory drugs for the treatment of Alzheimer's disease. Lancet Neurol, 2002; 1: 279-84.
4. Akter K, Lanza EA, Martin SA, Myronyuk N, Rua M, Raffa RB. Diabetes mellitus and Alzheimer's disease: shared pathology and treatment. Br J Clin Pharmacol, 2011; 71: 365-76.
5. Allam AR, Sridhar GR, Thota H, Babu CS, Prasad AS, Divakar C. Alzheimer's disease and type 2 diabetes mellitus: the cholinesterase connection? Lipids Health Dis., 2006; 5: 28.
6. American Diabetes Association. Standards of medical care in diabetes - 2013. Diabetes Care, 2013; 36: 11- 66.
7. Aranda-Orgilles B, Rutschow D, Zeller R, Karagiannidis AI, Kohler A, Chen C, et al. Protein phosphatase 2A (PP2A)-specific ubiquitin ligase MID1 is a sequence-dependent regulator of translation efficiency controlling 3-phosphoinositide- dependent protein kinase-1 (PDPK-1). J Biol Chem., 2011; 286: 39945-57.
8. Bakris GL, Fonseca VA, Sharma K, Wright EM. Renal sodium glucose transport: role in diabetes and potential clinical implications. Kidney Int, 2009; 75: 1272-7.
9. Banks WA, Kastin AJ, Maness LM, Huang W, Jaspan JB. Permeability of the blood-brain barrier to amylin. Life Sci., 1995; 57: 1993-2001. Biessels GJ, Deary IJ, Ryan CM. Cognition and diabetes: A lifespan perspective. Lancet Neurol, 2008; 7: 184-90.
10. Calissano P, Matrone C, Amadoro G. Apoptosis and in vitro Alzheimer disease neuronal models. Commun Integr Biol., 2009; 2: 163-9.
11. Carrotta R, Di Carlo M, Manno M, Montana G, Picone P, Romancino D, et al. Toxicity of recombinant beta-amyloid prefibrillar oligomers on the morphogenesis of the sea urchin Paracentrotus lividus. FASEB J., 2006; 20: 1916-7.
12. Ceconi C, Francolini G, Bastianon D, Gitti GL, Comini L, Ferrari R. Differences in the effect of angiotensin-converting enzyme inhibitors on the rate of endothelial cell apoptosis: In vitro and in vivo studies. Cardiovasc Drugs Ther., 2007; 21: 423-9.
13. Ceriello A, Piconi L, Quagliaro L, Wang Y, Schnabel CA, Ruggles JA, et al. Effects of pramlintide on postprandial glucose excursions and measures of oxidative stress in patients with type 1 diabetes. Diabetes Care, 2005; 28: 632-7.

14. Cernea S, Raz I. Intranasal insulin: PK profile designed specifically for prandial treatment of Type 2 Diabetes. Drugs Today, 2006; 42: 405-24.
15. Chen Y, Zhou K, Wang R, Liu Y, Kwak YD, Ma T, et al. Antidiabetic drug metformin (GlucophageR) increases biogenesis of Alzheimer's amyloid peptides via up-regulating BACE1 transcription. Proc Natl Acad Sci USA, 2009; 106: 3907-12.
16. Christensen M, Knop FK, Vilsboll T, Holst JJ. Lixisenatide for type 2 diabetis mellitus. Expert Opin Investig Drugs, 2011; 20: 549-57.
17. Craft S, Saunders AM, Altman JF, Ormandy GC, Craft S, Foley IM, et al. Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. Pharmacogenomics J., 2006; 6: 246-54.
18. Craft S, Baker LD, Montine TJ, Minoshima S, Watson GS, Claxton A, et al. Intranasal insulin therapy for Alzheimer disease and amnestic mild cognitive impairment: a pilot clinical trial. Arch Neurol, 2012; 69: 29-38.
19. Cuesta S, Kireev R, Forman K, García C, Escames G, Ariznavarreta C, et al. Melatonin improves inflammation processes in liver of senescence-accelerated prone male mice (SAMP8). Exp Gerontol, 2010; 45: 950-6.
20. De Felice FG, Vieira MNN, Bomfim TR, Decker H, Velasco PT, Lambert MP, et al. Protection of synapses against Alzheimer's-linked toxins: Insulin signaling prevents the pathogenic binding of Abeta oligomers. Proc Natl Acad Sci USA, 2009; 106: 1971-6.
21. Di Carlo M, Picone P, Carrotta R, Giacomazza D, San Biagio PL. Insulin promotes survival of amyloid-beta oligomers neuroblastoma damaged cells via caspase 9 inhibition and Hsp70 upregulation. J Biomed Biotechnol, 2010; 2010: 8.
22. During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med., 2003; 9: 1173-9.
23. Edward CC, Robert RH. SGLT2 inhibition-a novel strategy for diabetes treatment. Nat Rev Drug Discov, 2010; 1-9.
24. El-Mir MY, Detaille D, Delgado-Esteban M, Guigas B, Attia S, Fontaine E, et al. Neuroprotective role of antidiabetic drug metformin against apoptotic cell death in primary cortical neurons. J Mol Neurosci, 2008; 34: 77-87.
25. Escribano L, Simon AM, Perez-Mediavilla A, Salazar-Colocho P, Del Rio J, Frechilla D. Rosiglitazone reverses memory decline and hippocampal glucocorticoid receptor down-

regulation in an Alzheimer's disease mouse model. Biochem Biophys Res Commun, 2009; 379: 406-10.

26. Exalto L, Whitmer R, Kappele L, Biessels G. An update on type 2 diabetes, vascular dementia and Alzheimer's disease. Exp Gerontol, 2012; 47: 858-64.
27. Faludi P, Brodows R, Burger J, Ivanyi T, Braun DK. The effect of exenatide re exposure on safety and efficacy. Peptides, 2009; 30: 1771-4.
28. Farret A, Lugo-Garcia L, Galtier F, Gross R, Petit P. Pharmacological inter-ventions that directly stimulate or modulate insulin secretion from pancreatic betacell: implications for the treatment of type 2 diabetes. Fundam Clin Pharmacol, 2005; 19: 647-56.
29. Fukuen S, Iwaki M, Yasui A, Makishima M, Matsuda M, Shimomura I. Sulfonylurea agents exhibit peroxisome proliferator-activated receptor gamma agonistic activity. J Biol Chem., 2005; 280: 23653-9.
30. Garcia-Bueno B, Madrigal JL, Lizasoain I, Moro MA, Lorenzo P, Leza JC. Peroxisome proliferator-activated receptor gamma activation decreases Neuroinflammation in brain after stress in rats. Biol Psychiatry, 2005; 57: 885-94.
31. Gedulin BR, Rink TJ, Young AA. Dose-response for glucagon static effect of amylin in rats. Metabolism, 1997; 46: 67-70.
32. Gengler S, McClean P, McCurtin R, Gault V, Holscher C. Val(8)GLP-1 rescues synaptic plasticity and reduces dense core plaques in APP/PS1 mice. Neurobiol Aging, 2012; 33: 265-76.
33. Gray E, Ginty M, Kemp K, Scolding N, Wilkins A. The PPAR-gamma agonist pioglitazone protects cortical neurons from inflammatory mediators via improvement in peroxisomal function. J Neuroinflammation, 2012; 9: 63.
34. Joshi P, Tanwar O, Rambhade S, Bhaisare M, Jain D. 2-D QSAR studies of steroidal natural products oleanic acid and their semisynthetic derivatives as potent protein tyrosine phosphatase1B inhibitors. Med Chem Res., 2012; 21: 351–356.
35. Greenberg DA, Jin K. Neurodegeneration and neurogenesis: focus on Alzheimer's disease. Curr Alzheimer Res., 2006; 3: 25-8.
36. Gupta A, Bisht B, Dey CS. Peripheral insulin-sensitizer drug metformin ameliorates neuronal insulin resistance and Alzheimer's-like changes. Neuropharmacology, 2011; 60: 910-20.
37. Hamilton A, Patterson S, Porter D, Gault VA, Holscher C. Novel GLP-1 mimetics developed to treat type 2 diabetes promote progenitor cell proliferation in the brain. J Neurosci Res., 2011; 89: 481-9.

38. Hardy J, Allsop D. Amyloid deposition as the central event in the aetiology of Alzheimer's disease. Trends Pharmacol Sci., 1991; 12: 383-8.
39. Harrington C, Sawchak S, Chiang C, Davies J, Saunders A, Irizarry M, et al. Effects of rosiglitazoneextended release as adjunctive therapy to acetylcholinesterase inhibitors over 48 weeks on cognition in Apoe4-stratified subjects with mild-to-moderate Alzheimer's disease. Alzheimer Dement, 2009; 5: 17-8.
40. Heneka MT, Landreth GE, Feinstein DL. Role for peroxisome proliferator-activated receptor-gamma in Alzheimer's disease. Ann Neurol, 2001; 49: 276.
41. Heneka MT, Sastre M, Dumitrescu-Ozimek L, Hanke A, Dewachter I, Kuiperi C, et al. Acute treatment with the PPARgamma agonist pioglitazone and ibuprofen reduces glial inflammation and Abeta 1–42 levels in APPV717I transgenic mice. Brain, 2005; 128: 1442-53.
42. Hilder TL, Baer LA, Fuller PM, Fuller CA, Grindeland RE, Wade CE, et al. Insulin-independent pathways mediating glucose uptake in hind limb-suspended skeletal muscle. J Appl Physiol, 2005; 99: 2181-8.
43. Ho L, Osaka H, Aisen PS, Pasinetti GM. Induction of cyclooxygenase (COX)-2 but not COX-1 gene expression in apoptotic cell death. J Neuroimmunol, 1998; 89: 142-9.
44. Holscher C, Li L. New roles for insulin-like hormones in neuronal signalling and protection: New hopes for novel treatments of Alzheimer's disease? Neurobiol Aging, 2010; 31: 1495-502.
45. Hsu CC, Wahlqvist ML, Lee MS, Tsai HN. Incidence of dementia is increased in type 2 diabetes and reduced by the use of sulfonylureas and metformin. J Alzheimers Dis., 2011; 24: 485-93.
46. Hwang IK, Kim IY, Joo EJ, Shin JH, Choi JW, Won MH, et al. Metformin normalizes type 2 diabetesinduced decrease in cell proliferation and neuroblast differentiation in the rat dentate gyrus. Neurochem Res., 2010; 35: 645-50.
47. Jackson K, Barisone GA, Diaz E, Jin LW, DeCarli C, Despa F. Amylin deposition in the brain: A second amyloid in Alzheimer disease? Ann Neurol, 2013; 74: 517-26.
48. Jankowsky JL, Slunt HH, Ratovitski T, Jenkins NA, Copeland NG, Borchelt DR. Co-expression of multiple trans genes in mouse CNS: a comparison of strategies. Biomol Eng, 2001; 17: 157-65.
49. Ji H, Wang H, Zhang F, Li X, Xiang L, Aiguo S. PPARgamma agonist pioglitazone inhibits microglia inflammation by blocking p38 mitogen activated protein kinase signaling pathways. Inflamm Res., 2010; 59: 921-9.

50. Jiang Q, Heneka M, Landreth GE. The role of peroxisome proliferator-activated receptor-gamma (PPARgamma) in Alzheimer's disease: therapeutic implications. CNS Drugs, 2008; 22: 1-14.
51. Kickstein E, Krauss S, Thornhill P, Rutschow D, Zeller R, Sharkey J, et al. Biguanide metformin acts on tau phosphorylation via mTOR/protein phosphatase 2A (PP2A) signaling. Proc Natl Acad Sci USA., 2010; 107: 21830-5.
52. Kirpichnikov D, McFarlane SI, Sowers JR. Metformin: an update. Ann Intern Med., 2002; 137: 25-33.
53. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med., 2002; 346: 393-403.
54. Kochanek KD, Xu J, Murphy SL, Minino AM, Kung HC. Deaths: Preliminary data for 2009. Natl Vital Stat Rep., 2011; 59: 1-51.
55. Kosaraju J. Neuroprotective effects of vildagliptin, a dipeptidyl peptidase 4 inhibitor against streptozotocin induced Alzheimer's disease. J Neurol Neurophysiol, 2013; 4: 3.
56. Krauss S, Griesche N, Jastrzebska E, Chen C, Rutschow D, Achmüller C, et al. Translation of HTT mRNA with expanded CAG repeats is regulated by the MID1-PP2A protein complex. Nat Commun, 2013; 4: 1511.
57. Łabuzek K, Suchy D, Gabryel B, Bielecka A, Liber S, Okopień B. Quantification of metformin by the HPLC method in brain regions, cerebrospinal fluid and plasma of rats treated with lipopolysaccharide. Pharmacol Rep., 2010; 62: 956–65.
58. Landreth G. Therapeutic use of agonists of the nuclear receptor PPARγ in Alzheimer's disease. Curr Alzheimer Res., 2007; 4: 159-64.
59. Lee HK, Kumar P, Fu Q, Rosen KM, Querfurth HW. The insulin/Akt signaling pathway is targeted by intracellular beta amyloid. Mol Biol Cell., 2009; 20: 1533-44.
60. Li L, Holscher C. Common pathological processes in Alzheimer disease and type 2 diabetes: a review. Brain Res Rev., 2007; 56: 384-402.
61. Liu F, Wang Y, Yan M, Zhang L, Pang T, Liao H. Glimepiride attenuates Aβ production via suppressing BACE1 activity in cortical neurons. Neurosci Lett., 2013; 557: 90-4.
62. McClean PL, Parthsarathy V, Faivre E, Hölscher C. The diabetes drug liraglutide prevents degenerative processes in a mouse model of Alzheimer's disease. J Neurosci, 2011; 31: 6587-94.
63. Messier C, Gagnon M. Cognitive decline associated with dementia and type 2 diabetes: The interplay of risk factors. Diabetologia, 2009; 52: 2471-4.

64. Mielke JG, Taghibiglou C, Wang YT. Endogenous insulin signaling protects cultured neurons from oxygen-glucose deprivation-induced cell death. Neuroscience, 2006; 143: 165-73.
65. Mihaylova MM, Shaw RJ. The AMPK signalling pathway coordinates cell growth, autophagy and metabolism. Nat Cell Biol., 2011; 13: 1016-23. Mitsukawa T, Takemura J, Asai J, Nakazato M, Kangawa K, Matsuo H, et al. Islet amyloid polypeptide response to glucose, insulin, and somatostatin analogue administration. Diabetes, 1990; 39: 639-42.
66. Moon HS, Chamberland JP, Diakopoulos KN, Fiorenza CG, Ziemke F, Schneider B, et al. Leptin and amylin act in an additive manner to activate overlapping signaling pathways in peripheral tissues: in vitro and ex vivo studies in humans. Diabetes Care, 2011; 34: 132-8.
67. Morley JE, Farr SA, Kumar VB, Armbrecht HJ. The SAMP8 mouse: a model to develop therapeutic interventions for Alzheimer's disease. Curr Pharm Des., 2012; 18: 1123-30.
68. Murphy S. Production of nitric oxide by glial cells: Regulation and potential roles in the CNS. Glia, 2000; 29: 1-13.
69. Murphy MP, Chen KC, Blalock EM, Landfield PW, Porter NM, Thibault O. Long-term pioglitazone treatment improves learning and attenuates pathological markers in a mouse model of Alzheimer's Disease. J Alzheimers Dis., 2012; 30: 943-61.
70. Nath N, Khan M, Paintlia MK, Singh I, Hoda MN, Giri S. Metformin attenuated the autoimmune disease of the central nervous system in animal models of multiple sclerosis. J Immunol, 2009; 182: 8005-14.
71. Nicolakakis N, Aboulkassim T, Ongali B, Lecrux C, Fernandes P, Rosa-Neto P, et al. Complete rescue of cerebrovascular function in aged Alzheimer's disease transgenic mice by antioxidants and pioglitazone, a peroxisome proliferator-activated receptor gamma agonist. J Neurosci, 2008; 28: 9287-96.
72. Nolte MS, Taboga C, Salamon E, Moses A, Longenecker J, Flier J, et al. Biological activity of nasally administered insulin in normal subjects. Horm Metab Res., 1990; 22: 170-4.
73. Park S. A common pathogenic mechanism linking type-2 diabetes and Alzheimer's disease: evidence from animal models. J Clin Neurol, 2011; 7: 10-8.
74. Pedersen WA, McMillan PJ, Kulstad JJ, Leverenz JB, Craft S, Haynatzki GR. Rosiglitazone attenuates learning and memory deficits in Tg2576 Alzheimer mice. Exp Neurol, 2006; 199: 265-73.

75. Perry T, Lahiri DK, Sambamurti K, Chen D, Mattson MP, Egan JM, et al. Glucagon-like peptide-1 decreases endogenous amyloid-beta peptide (Abeta) levels and protects hippocampal neurons from death induced by Abeta and iron. J Neurosci Res., 2003; 72: 603-12.
76. Perry T, Holloway HW, Weerasuriya A, Mouton PR, Duffy K, Mattison JA, et al. Evidence of GLP-1- mediated neuroprotection in an animal model of pyridoxine-induced peripheral sensory neuropathy. Exp Neurol, 2007; 203: 293-301.
77. Picone P, Carrotta R, Montana G, Nobile MR, San Biagio PL, Di Carlo M. Abeta oligomers and fibrillar aggregates induce different apoptotic pathways in LAN5 neuroblastoma cell cultures. Biophys J., 2009; 96: 4200-11.
78. Picone P, Giacomazza D, Vetri V, Carrotta R, Militello V, San Biagio PL, et al. Insulin-activated Akt rescues Aβ oxidative stress-induced cell death by orchestrating molecular trafficking. Aging Cell, 2011; 10: 832-43.
79. Potes CS, Boyle CN, Wookey PJ, Riediger T, Lutz TA. Involvement of the extracellular signal-regulated kinase 1/2 signaling pathway in amylin's eating inhibitory effect. Am J Physiol Regul Integr Comp Physiol, 2012; 302: 340-51.
80. Priyadarshini M, Kamal MA, Greig NH, Realef M, Abuzenadah AM, Chaudhary AG, et al. Alzheimer's disease and type 2 diabetes: exploring the association to obesity and tyrosine hydroxylase. CNS Neurol Disord Drug Targets, 2012; 11: 482-9.
81. Rajesh R, Naren P, Vidyasagar S, Unnikrishnan M, Pandey S, Varghese M. Sodium Glucose Co transporter 2 (SGLT2) inhibitors: a new sword for the treatment of Type 2 Diabetes Mellitus. Int J Pharm Sci Res., 2010; 1: 139-47.
82. Rensink AA, Otte-Holler I, de Boer R, Bosch RR, ten Donkelaar HJ, de Waal RM, et al. Insulin inhibits amyloid beta- induced cell death in cultured human brain pericytes. Neurobiol Aging, 2004; 25: 93-103.
83. Rizvi SMD, Shakil S, Biswas D, Shakil S, Shaikh S, Bagga P, et al. Invokana (Canagliflozin) as a dual inhibitor of Acetylcholinesterase and Sodium Glucose Co-Transporter 2: advancement in Alzheimer's Disease-Diabetes Type 2 linkage via an Enzoinformatics study. CNS Neurol Disord Drug Targets, 2014; 13: 447-51.
84. Rodriguez-Rivera J, Denner L, Dineley KT. Rosiglitazone reversal of Tg2576 cognitive deficits is independent of peripheral gluco-regulatory status. Behav Brain Res., 2011; 216: 255-61.

85. Ronnemaa E, Zethelius B, Sundelöf J, Sundström J, Degerman-Gunnarsson M, Berne C, et al. Impaired insulin secretion increases the risk of Alzheimer disease. Neurology, 2008; 71: 1065-71.
86. Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. Neurobiol Aging, 2011; 32: 1626-33.
87. Sayre LM, Zelasko DA, Harris PL, Perry G, Salomon RG, Smith MA. 4-Hydroxynonenal-derived advanced lipid peroxidation end products are increased in Alzheimer's disease. J Neurochem, 1997; 68: 2092-7.
88. Scarsi M, Podvinec M, Roth A, Hug H, Kersten S, Albrecht H, et al. Sulfonylureas and glinides exhibit peroxisome proliferator-activated receptor gamma activity: a combined virtual screening and biological assay approach. Mol Pharmacol, 2007; 71: 398-406.
89. Schipper HM, Cissé S, Stopa EG. Expression of heme oxygenase-1 in the senescent and Alzheimer-diseased brain. Ann Neurol, 1995; 37: 758-68.
90. Sexton PM, Paxinos G, Kenney MA, Wookey PJ, Beaumont K. In vitro autoradiographic localization of amylin binding sites in rat brain. Neuroscience, 1994; 62: 553-67.
91. Shaikh S, Rizvi SMD, Shakil S, Riyaz S, Biswas D, Jahan R. Forxiga (Dapagliflozin): Plausible role in the treatment of diabetes associated neurological disorders. Biotechnol Applied Biochem, 2014. [epub ahead of print] DOI: 10.1002/bab.1319.
92. Steen E, Terry BM, Rivera EJ, Cannon JL, Neely TR, Tavares R, et al. Impaired insulin and insulin-like growth factor expression and signaling mechanisms in Alzheimer's disease – is this type 3 diabetes? J Alzheimers Dis., 2005; 7: 63-80.
93. Testa MA, Simonson DC. Health economic benefits and quality of life during improved glycemic control in patients with type 2 diabetes mellitus: a randomized, controlled, double-blind trial. JAMA, 1998; 280: 1490-6.
94. To AW, Ribe EM, Chuang TT, Schroeder JE, Lovestone S. The epsilon3 and epsilon4 alleles of human APOE differentially affect tau phosphorylation in hyper insulinemic and pioglitazone treated mice. PLoS One, 2011; 6: e16991.
95. Watson GS, Cholerton BA, Reger MA, Baker LD, Plymate SR, Asthana S, et al. Preserved cognition in patients with early Alzheimer disease and amnestic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. Am J Geriatr Psychiatry, 2005; 13: 950-8.

96. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. Neurology, 2008; 71: 1057-64.
97. Wisniewski HM, Frackowiak J. Differences between the pathogenesis of senile plaques and congophilic angiopathy in Alzheimer disease. J Neuropathol Exp Neurol, 1998; 57: 96-8.
98. Zang M, Zuccollo A, Hou X, Nagata D, Walsh K, Herscovitz H, et al. AMP-activated protein kinase is required for the lipid-lowering effect of metformin in insulin-resistant human HepG2 cells. J Biol Chem., 2004; 279: 47898-905.
99. Zhao WQ, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ, et al. Amyloid beta oligomers induce impairment of neuronal insulin receptors. FASEB J., 2008; 22: 246-60.