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Review

Efficacy and risk profile of anti-diabetic therapies: Conventional vs traditional drugs—A mechanistic revisit to understand their mode of action

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ABSTRACT

An increasing array of anti-diabetic drugs are available today, yet Type-2 diabetes mellitus (T2DM) – remains a life threatening disease, causing high mortality and morbidity in developing and developed countries. As of now, no effective therapy is available for the complete eradication/cure of diabetes and its associated complications. Therefore, it is time to re-think and revisit molecular pathways and targets of each existing drug in order to identify multiple targets from different signaling pathways that may be manipulated simultaneously to treat or manage T2DM effectively. Bearing this goal in mind, the article reviews the mechanisms of action of available anti-diabetic drugs with in-depth mechanistic analysis of each therapy. The conventional and herbal strategies are analysed and compared for their benefits and the associated possible side effects. This critical information is necessary not only for the development of

Abbreviations: GLUT, Glucose transporter; T1DM, Type-1 diabetes mellitus; T2DM, Type-2 diabetes mellitus; PKB/Akt, protein kinase B; GSK-3, glycogen synthase kinase-3; PGC-1α, peroxisome proliferator-activated receptor gamma coactivator-1α; FOXO, forkhead box O; VLDL, very low density lipoprotein; cAMP, cyclic AMP; PKA, protein kinase A; AMPK, AMP activated protein kinase; Hb A_{1C}, glycosylated haemoglobin A_{1C}; LKB-1, liver kinase B-1; CaM, Calmodulin; CaMKKβ, CaM kinase-β; CREB, cAMP response element binding protein; TORC2, transducer of regulated CREB-activity 2; PEPCK, phosphoenol pyruvate carboxykinase; G6Pase, glucose-6 phosphatase; SIRTI, silent mating type information regulator 2 homolog 1; GCN5, general control nonderepressible 5; SREBP-1, sterol regulatory element-binding proteins 1; ACC, acetyl-CoA carboxylase; FAS, fatty acid synthase; PK, pyruvate kinase; IRS-1, insulin receptor substrate-1; PI3 K, phosphatidylinositide 3-kinase; p38 MAPK, p38 mitogen-activated protein kinase; Rab-GAP, Rab guanosine triphosphatase-activating protein also called AS160; HK, hexokinase; Glc-6-P, glucose-6-phosphate; Gly Ph, glycogen phosphorylase; Ph K, phosphorylase kinase; GS, glycogen synthase; IL-1β, interleukine-1β; TNF-α, tumor necrosis factor-α; NFκB, nuclear factor kappa B; GLP-1, glucagon like peptide-1; GIP, glucose-dependent insulinotropic polypeptide; PPAR, peroxisome proliferator-activated receptor; GSV, GLUT-4 storage vesicles; TZD, Thiazolidinediones; FDA, food and drug administration; FFA, free fatty acids; PDH, pyruvate dehydrogenase; TCA, tricarboxylic acid cycle; PFK-1, phosphofructose kinase-1; PPRE, PPARγ-responsive elements; FATP, fatty acid transport protein; FAT, fatty acid translocase; CD36, cluster of differentiation 36; RXR, retinoid X receptor; NO, nitric oxide; AdipoR, adiponectin receptors; CRTC, CREB regulated transcriptional coactivator; aPKC, atypical protein kinase C; HNF-1α, hepatocytes nuclear factor −1α; K_{ATP}, ATP-sensitive K^+ channels; GIIS, glucose induces insulin secretion; SUR, sulphonylurea receptor; ABC, ATP-binding cassette; Kir6.x, K^+ channels; LC-CoA, long chain acyl-CoA; VDCC, voltage-dependent Ca^{2+} channels; PIP, phosphatidylinositide; Epac, exchange protein activated by cAMP; PFK-2/F2,6-BPase, phosphofructokinase-2/fructose2,6-bisphosphatase; NSU, non-sulfonylurea; RyR, ryanodine receptor; CICR, Ca^{2+}-induced Ca^{2+} release; DPP-4, dipeptidyl peptidase-4; Ex-4, Exenatide; TRPM2, trans-membrane receptor potential melastatin 2; NSCC, permeable non-selective cation channels; PLC, phospholipase C; DAG, diacyl glycerol; IP3, inositol-1,4,5-triphosphate; IP3-R, IP3-receptor; SER, smooth endoplasmic reticulum; PKC, protein kinase C; Rim2, Rab3-interacting molecules; ODN, oligodeoxynucleotides; GK, glucokinase; PDX-1, pancreatic and duodenal homeobox 1; IPF-1, insulin promoter factor 1; GLP-1R, GLP-1 receptor; BAD, Bcl-2-associated death promoter; PNPLA3, Patatin-like phospholipase domain-containing protein 3; ADA, adenosine deaminase; PTP1 B, protein tyrosine phosphatase 1B; ANP, atrial natriuretic; BNP, b-type ventricular natriuretic peptides; VMH, ventromedial nucleus; SGLT2, sodium glucose co-transporter 2; PTC, proximal tubular cells; PCT, proximal tubule epithelial cells; GFR, glomerular filtration rate; TmG, tubular max for glucose; SGK1, serum-glucocorticoids inducible kinase-1; SKT1, Succinyl-CoA:3-ketoacid-coenzyme A transferase; TC, tubular cells; ODC, ornithine decarboxylase; cPLA, Cytosolic phospholipase A; FBPase, fructose-1,6-bisphosphatase; EGP, endogenous glucose production; AGE, advanced glycation end products; RAGE, receptor of AGE; ROS, reactive oxygen species; ACE, angiotensin converting enzyme; EMA, European Medicines Agency; AGI, α-glucosidase inhibitors; PPHG, post prandial hyperglycemia; IAPP, islet amyloid polypeptide; CPT-1, carnitine palmitoyl transferase-1; STZ, streptozotocin; PTP1 B, protein tyrosine phosphatase 1B; SCD1, Stearoyl-CoA desaturase-1; NRF-1, nuclear respiratory factor-1; COX-4, Cyclooxygenase-4; F1,6BPase, fructose-1,6-phosphotase; CRA, corosolic acid; TA, Tannic acid; ERK, extracellular regulatory kinase; 4-hydroxyisoleucine, HIl; SOD, superoxide dismutase; PTEN, Phosphatase and tensin homolog.

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Rosiglitazone (PubChem CID: 77999)
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Repaglinide (PubChem CID: 65981)
Nateglinide (PubChem CID: 5311309)
Sitagliptin (PubChem CID: 4369359)
Vildagliptin (PubChem CID: 6918537)
Saxagliptin (PubChem CID: 11243969)
Linagliptin (PubChem CID: 10096344)
Alogliptin (PubChem CID: 11450633)
Teneligliptin (PubChem CID: 11949652)
Exenatide (PubChem CID: 56927919)
Liraglutide (PubChem CID: 16134956)
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Taspoglutide (PubChem CID: 56842233)
Phlorizin (PubChem CID: 6072)
Canagliflozin (PubChem CID: 24812758)
Dapagliflozin (PubChem CID: 9887712)
Acarbose (PubChem CID: 41774)
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Dipeptidyl peptidase-4 inhibitors
SGLT2
Phyto-drugs
miRNAs

better, novel and potent anti-diabetic therapy in future but also for best possible combinational therapies and strategies with the available drugs.

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