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Synthetic molecules applied in the treatment of type 2 diabetes

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ABSTRACT

Diabetes is considered a multifactorial disease that afflicts populations of the most diverse classes worldwide, being among the main health problems today. Among the types of diabetes, type 2 diabetes mellitus (DM-2) is considered the most prevalent pathology. This is due to the direct relationship between the cause of this disease and people's eating behavior. These factors justify the growing search for the development of drugs for DM-2, given that current drugs act on targets that are not very efficient for the treatment. Therefore, the objective of this review is to evaluate the progress of research related to the search for new synthetic drugs for a more selective treatment for DM-2. The researches were searched in the main academic databases (National Center for Biotechnology Information (NCBI), Science Direct and Google Scholar), and research tools such as Drug Bank and Clinical Trials. Seventy articles were selected that were causally related to the descriptors used. According to the survey, about 60 compounds of synthetic origin were found and present in the various phases of the study and some molecules already approved for use. A variety of strategies and new therapies related to DM-2 grows each year, as new targets involved are elucidated. Therefore, it is possible to envision a promising future for the treatment of DM-2. because studies like this show the evolution of biochemical research methods and the advances in medicinal chemistry, it will be possible in the future that a multifactorial disease of this type can be treated in a specific way for each patient.

Keywords: Synthetic drugs, Type 2 Diabetes Mellitus, New treatment strategies.

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Introduction

Diabetes is a multifactorial disease that afflicts populations of the most diverse classes worldwide. In addition, it is being among the main health problems today. This disease is characterized by a serum elevation of glucose levels, which is due to distinct dysfunctions that prevent this substance from being directed to cells. Whereas, these cells use this molecule as the main resource for carrying out vital functions in an organism. Thus, extracellular excess and the absence of sufficient amounts of glucose in the intracellular environment can promote a variety of disorders. Also, this can aggravate homeostasis in the long run and to lead to serious health problems[1-4].

Due to the multifactorial complexity and the diverse etiological factors, diabetes has a heterogeneity in relation to the main causative factor. This may be due to metabolic, hormonal, renal or immunological disorders. Based on this knowledge, diabetes can be classified into mellitus (type 1 or type 2), gestational, or insipidus (nephrogenic or central). Among the types of diabetes mellitus, type 2 diabetes (DM-2) is the most prevalent pathology worldwide. Direct relationship between the cause of this disease and eating behavior is identified as one of the biggest risk factors for its development[5-7].

Besides to epidemiological factors, the number of patients affected by other types of diabetes is much lower when compared to DM-2. This is due to genetic factors being more prevalent in the etiology of other types. DM-2 can be developed by a wide variety of factors that alter several biochemical routes, which has been increasingly investigated during the pathophysiological studies of the disease. This can provide greater insights on the main protein targets involved[7-9].

These facts justify the growing search for the development of drugs for DM-2, in which the current drugs act on targets that are not very efficient for the treatment. In addition, research over the years has shown other increasingly promising biomacromolecules, which can be modulated to enhance the effects of pharmacotherapy already used. As well as, to promoting a more selective treatment for each case involving DM-2[10,11]. Therefore, the objective of this review is to evaluate the progress of research related to the search for new synthetic drugs for a more selective treatment for DM-2.

Methodology

This chapter is a bibliographic review using articles published between 2010 and 2020. The researches were searched in the main academic databases (National Center for Biotechnology Information (NCBI), Science Direct and Google Scholar) and research tools such as Drug Bank and Clinical Trials. About 35 articles were selected that were causally related to the following descriptors used: synthetic drugs, type 2 diabetes mellitus, new treatment strategies. About 35 articles were selected in which they were related to the following descriptors used: synthetic drugs, type-2 diabetes mellitus, new treatment strategies. The search was conducted between April and May 2020

Results and discussion

Pathophysiological mechanisms of type 2 diabetes

Well-established studies describe that the emergence of DM-2 results mainly from the increased resistance of insulin receptors (IRS-1), which are distributed in all tissues of the body. Consequently, even if insulin is secreted in sufficient quantities, its biological response ends up being less effective. In some cases, there is loss of activity due to the internalization of receptors in target tissues[12].

In addition, another well-established factor is the direct relationship between DM-2 and obesity. Whereas, several etiological studies have shown that weight gain is one of the main risk factors for the development of this disease. Pathophysiological studies explain that the increase in lipid levels promotes greater resistance of the IRS to insulin. Since 1985, Obesity is also considered as a disease. It is defined

as a pathological condition characterized by excessive accumulation of fat disproportionately to height, gender, and age [13,14].

The proof of the secretory function of adipose tissue was what made it possible to justify the correlation between obesity and DM-2. These studies showed that hormonal substances called cytokines, which were already extensively investigated for their participation in the immune response, were also secreted by the cells of the adipose tissue. Thus, the specific cytokines of that tissue were classified as adipokines[15,16].

When individuals are overweight, a lot of cytokines of lipid origin is released into the bloodstream. This can cause an increase in the production of pro-inflammatory factors. One of these factors is the tumor necrosis factor alpha (TNF-α), which is one of the main pro-inflammatory cytokines in the body. Studies have proven the role of this substance in the development of diabetes. Since, the excess of fatty acids stimulates the release of TNF-α, either from the tissue itself or from adjacent tissues[16]. Subsequently, this cytokine ends up directly interfering with the action of insulin through several pathways, which are: repression of insulin receptor transcription, increased secretion of fatty acids, reduced secretion of anti-inflammatory adipokines such as adiponectin, and also by decreased ability to translocation of GLUT-4 receptors via insulin receptor phosphorylation (IRS-1) [3,10,12,13,16-19].

Obesity is also responsible for the increased expression of the enzyme Dipeptidyl-dipeptidase-4 (DPP-4), which has the function of cleaving the peptide similar to glucagon type 1 (GLP-1). In addition, the increase in serum levels of this protein promotes a depletion of blood GLP-1 levels that are responsible for carrying out the glucose stock in cells during feeding[20].

Advances in the treatment of type 2 diabetes

Increase in morbidity due to DM-2 results from the lack of new therapeutic strategies for its treatment, as many patients do not have access to the most widespread pharmacological approaches in the clinical scope. This fact justifies the growing search for new substances that are capable to potentiating the effects of the treatment as well as reducing the associated side effects[21,22].

The development of new substances has been done based on a rational planning, in which it assesses all variables related to the efficacy and safety of the medication[21,22]. Due to the advances made on the pathophysiological mechanisms of DM-2, a variety of possible new targets have emerged. Whereas these targets are related to the disease development process[23]. However, despite advances in the understanding of the risks involved in DM-2, most new substances launched on the pharmaceutical market are considered me-too drugs. They only promote improvements in the pharmacokinetic properties of existing drugs[24].

Recently developed synthetic compounds for the treatment of type 2 diabetes

According to the survey, about 60 compounds of synthetic origin were found. These substances are present in the various study phases, and there are some molecules already approved for use, as shown in table 1

DPP4 inhibitors

The vast majority of found compounds have as molecular targets, proteins related to the development of DM-2. In relation to the most investigated protein target, of the 60 found compounds, about 17 are targeting the DPP-4 enzyme, since this target is closely related to the pathophysiological mechanisms described above. In addition, most compounds found in our study that have been approved for clinical use are part of the DPP-4 inhibitor class. This shows that this protein is a very promising target[25-30].

GLP-1 analogs

GLP-1 analogs mimic the action of this peptide, which has the function of promoting an increase in insulin secretion, decreasing glucagon secretion via GCGR, increasing the sensitivity of insulin by its tissue receptors, inhibiting gastric emptying, and promoting satiety[31,32]. Eight com-

pounds were found to be possible mimetic peptides, with 2 compounds approved for clinical use (dulaglutide and semaglutide)[33,34] and another compound in study of phase III (taspoglutide).

Table 1. List of recent synthetic drugs found for the treatment of DM-2.

Found compounds	Pharmacological targts	Study phases	References
6-deoxy-O-spirocetal-C-aryl glycosides	SGLT2	In vitro, in vivo	40
Abn-CBD and AS-1269574	GPR119	In vivo	56
Alogliptin	DPP-4	Approved	45,57
2-oxaloacetate analogs	PTP1B	In vivo	
Anagliptin	DPP-4	Approved	58
GLP-1 analogs	GLP-1 Receptor	In vivo	31, 32
Xanthine, pyrimidinone and arylmethylamine analogs	DPP-4	In vitro	30
Carba-sugars	SGT2	In vitro	38
Copper-ethylenediamo complexes	Alpha-glycosidase PTP1B	In vitro	50, 51
Metal complexes derived from anthranilic acid	Alpha-glycosidase	In vitro	59
Vanadium complexes	PTP1B, ROS	In vivo	8, 51
Zinc complex	Insulinomimetic, PTP1B	In vivo	46, 53
DA-1241	GLP-1, GRP119	In vivo	73
Dapaglifozin	SGLT2	Approved	35
Starch derivatives	DPP-4	In vitro	60
N-glycosyl-indole derivatives	SGLT2	In vitro	39
Indazolic derivatives	GCGR	In vitro	61
Nicotine derivatives	PTP1B	In vitro	62
Derivatives phenylalanines	DPP-4	In vitro	63
Phenylethylamines, phenpropylamines and pyrimidinedionic derivatives	DPP-4	In vitro	30
Fullerene derivatives	PTP1B	In vitro	17, 47
Piperidine derivatives	DPP-4	In vitro	64
Pyrrole [2,3-c] azepine derivatives	PTP1B	In vitro	42
Pyrrolidine derivatives	DPP-4	In vitro	26
Pyrimido [5,4-d] pyrimidine derivatives	GPR119	In vivo	65
Prolylthiazolidine derivatives	DPP-4	In vitro	66
Derivatives-quinazolines + thiazolines	DPP-4	In vitro	28
Quinolonic derivatives	PTP1B	In vitro	49
Tetrazolic derivatives	PTP1B	In vitro	67, 68
Thiazolidine-2,4-dione derivatives	PTP1B	In vivo	50
Thiomorpholin derivatives	DPP-4	In vitro	69
Dulaglutide	GLP-1 Receptor	Approved	33
DS-8500a	GPR119	Phase II	70, 43
Elafibranor	PPAR	Phase II	51
Evogliptin	DPP-4	Approved	71
Furan-2-carbohydrazides	GCGR	In vitro	72
Gemigliptin	DPP-4	Approved	73
Gosogliptin	DPP-4	Approved	27
GRA1	GCGR	In vitro, in vivo, ex-vivo	74
HBK001	DPP-4, GPR119	In vivo	29
thiazole-cyclopentadiene hybrid	PTP1B	In vitro	62
Imeglimin	Mitochondrial membrane	Phase II	54, 55
Ipragliflozin	SGLT2	Approved	36
KY-226	PTP1B	In vivo	75
Linagliptin	DPP-4	Approved	76
LY2409021	GCGR	Phase II	77
LY3298176	GLP-1 Receptor	Phase II	11
MB-07803	FBPhase	Phase II	78
MD001	PPAR	In vitro, in vivo	18
Omarigliptin	DPP-4	Approved	79
Semaglutide	GLP-1 Receptor	Approved	34
Taspoglutide	GLP-1 Receptor	Phase III	80
Teneligliptin	DPP-4	Approved	81, 82
Trelagliptin	DPP-4	Approved	83
Trihidroxychalcones and trihidroxitrihidrochalcones	SGLT2	In vitro	37
TT-OAD2	GLP-1 Receptor	In vitro	84
TTP399	GK	Phase II	52
TTP273	GLP-1 Receptor	Phase II	85
YH18421	GPR119	In vivo	86
ZB-16 and derivates	GPR119	In vitro e in vivo	87

GLP-1 (glucagon-like peptide-1 receptor); DPP-4 (Dipeptidyl-peptidase-4); GK (Glycokinase); SGLT2 (Sodium-glucose co-transporter); GPR119 (G-protein-coupled-receptor-119); PTP1B (Protein-tyrosine phosphatase 1B); GCGR (Glucagon-receptor); PPAR (Peroxisome proliferator-activated receiver); FBPase (Fructose 1,6-bisphosphatase).

SGLT-2 channel inhibitors

The SGLT-2 channel is present in the proximal convolute tubule and is primarily responsible for glucose reabsorption using a cotransport with the sodium ion that is in favor of its gradient, while glucose is being transported against its gradient. Glucose reabsorption can be disadvantageous when the individual is in a situation of hyperglycemia; therefore, the use of inhibitors of this reabsorption channel is an alternative treatment that can be used in combination with other medications. Six found compounds are part of this category, with a recently approved compound (ipragliflozin)[35-40].

GPR119 receptor agonists

This G protein-coupled receptor is present on the surface of pancreatic cells and enterochromaffin cells, in which its activation stimulates insulin secretion by reducing blood glucose levels[29,41]. This type of alternative aims to promote a reduction in glucose levels gradually by reducing the risks of hypoglycemia cases, which is one of the effects widely reported in the drugs currently used. In our survey, we found about 7 compounds that possibly act by this route, where a substance (DS-8500a) is in phase II study[42,43].

PTP1B inhibitors

PTP1B is considered a non-tyrosine kinase receptor protein that acts through a cascade of downstream signaling. This culminates in the inactivation of insulin receptors via transcription factors 3 (STAT3) that are directed to the nucleus, inducing down regulation of these receptors. Use of inhibitors in this pathway is becoming increasingly relevant, in which it may be a new alternative for the development of insulin sensitizers that do not act through the PPAR-alpha pathway. In our study, about 12 compounds of organic (9) and inorganic (3) origin were found, all in the laboratory study phases[42,44-50].

PPAR-gamma agonists

Peroxisome proliferator-activated receptors, like PTP1B, functionate as proteins present in the intracellular environment, in which they act as transcription factors for differentiating fat cells. However, their role as a transcriptional signal is the opposite of this other protein. PPAR gamma indirectly increases the sensitivity of insulin receptors by increasing the uptake of fat by differentiated adipocytes. PPAR gamma increases the sensitivity of insulin receptors indirectly by increasing the uptake of fat by differentiated adipocytes, thus it reduces the release of desensitizing cytokines by increasing the uptake of fat and lipogenesis[16]. Only 2 compounds were found in our survey, one of which is in phase II clinical studies (elafibranor)[18,51].

Glucokinase (GK) activators

GK is a cytosolic enzyme that catalyzes the phosphorylation of glucose to glucose-6-phosphate during the process of glycogen synthesis, in which this phosphorylation decreases serum glucose levels. Therefore, the use of this enzyme in an allosteric form can reduce the excess glucose levels in the blood. Only one molecule of this class (TTP 399) was found in our study. However, this strategy looks very promising since this compound is already in phase II studies[52].

1,6-Fructose-bisphosphatase (FBPase) inhibitors

FBPase participates in the process of removing phosphate groups present in the fructose molecule, which is quickly isomerized to glucose. Thus, this enzyme ends up promoting an opposite effect to Glucokinase (GK) by raising up serum glucose levels. Based on this evidence, FBPase inhibitors have been developed, which can prevent dephosphorylation and subsequently isomerization. Only one molecule (MB-07803) was found for this target, which is in phase II studies[18,51].

Other targets investigated

Five found compounds were described acting on different targets than most seen in this survey. 4 of these compounds are metal complexes that promote actions that influence the metabolic behavior of the cell and / or regulate the production of reactive oxygen species (ROS). there is also a possible insulin-mimetic action that was

reported by one of the inorganic complexes (complex with iron). The other substance investigated is imenglimine, which has shown good results in phase II studies, but its molecular mechanism is still imprecise[46,53-55].

Conclusion

The search for new therapies related to DM-2 grows every year, as new targets involved are elucidated and a variety of strategies continue to be developed. Therefore, it is possible to envision a promising future for the treatment of DM-2. because studies like this show the evolution of biochemical research methods and the advances in medicinal chemistry, it will be possible in the future that a multifactorial disease of this type can be treated in a specific way for each patient.

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