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REVIEW ON IMIGLIMIN HYDROCHLORIDE

SAKSHI JADHAV

SAMEER ALI

SHRUTI VISHWAKARMA

ABU NEDAL SHAIKH

Under the Guidance

of

Pro. Nilam Nile

Chhatrapati Shivaji Maharaj University Panvel Navi Mumbai (Maharashtra)

ABSRACT

Imeglimin is the first in a new class of oral antidiabetic drug that can reduce reactive oxygen species production and increase mitochondrial DNA synthesis. Imeglimin is a novel anti-diabetic drug structurally related to metformin. Imeglimin tablets with a quick delivery recipe are presently being created and tried frequently. Imeglimin is the first medication in the glimin class of glucose-lowering medication. Evaluated the efficacy of imeglimin an glycemic control and insulin resistance improvement measured homeostatic model assessment insulin resistances. further studies are needed to evaluate whether imeglimin treatment could exert similar effect in vivo 2023 the authors.

KEYWORD

Imeglimin ,metformin, glimin, glycemic control

INTRODUCTION

Imeglimin is the first in a new tetrahydro triazine containing class of oral antidiabetic agents referred to as glimins. Its discovery was enabled by an in vivo phenotypic screen(based on antihyperglycaemic activity in rodents), followed by additional chemical modification of a lead molecule. Imeglimin is under investigation, with three pivotal phase 3 clinical trials having been recently completed in Japan.

Imeglimin is the first medication in the glimin class of glucose-lowering medications. A novel drug for the treatment of type 2 diabetes mellitus. With type 2 diabetes, addressing abnormalities in both insulin secretion

and sensitivity is a requirement for achieving optimal glucose management. Imeglimin,s distinct mode of action targets the three pathophysiologic elements of type 2 diabetes.

Type 2 diabetes is a widespread disease, affecting more than 500 million people worldwide. It is characterized by by chronic hyperglycaemia associated with various macrovascular complication. Diabetes is a growing public health issue worldwide; Japan is one of the nations most greatly impacted ,with 18.7 % of men and 9.3% of women 'in whom diabetes is strongly suspected . In Japan, diabetes has also been identified as a health care priority by the ministry of heath, Labour and welfare.

Imeglimin is a first-in-class novel oral antidiabetic agent to treat type 2 diabetes that was recently approved in June 2021 as a new oral antidiabetic drug by pharmaceuticals and medical devices agency in Japan. Its mode of action is distinct from all other antihyperglycaemic classes; imeglimin's underlying mechanism involves the targeting of mitochondrial bioenergetic and improving mitochondrial function. Imeglimin modulates mitochondrial respiratory chain complex activities while decreasing reactive oxygen species production. Imeglimin has been shown to amplify glucose-stimulated insulin secretion by improving beta-cell glucose responsiveness in patients with type 2 diabetes and to improve insulin sensitivity in a rodent model of diabetes, allowing for normalization of glucose tolerance. Recently, imeglimin has been shown to prevent the death of human endothelial cells by inhibiting opening of the mitochondrial permeability transition pore- a known cause a cell death without inhibiting mitochondrial respiration; this finding suggests the potential for end organ protection(e.g. kidney or heart).

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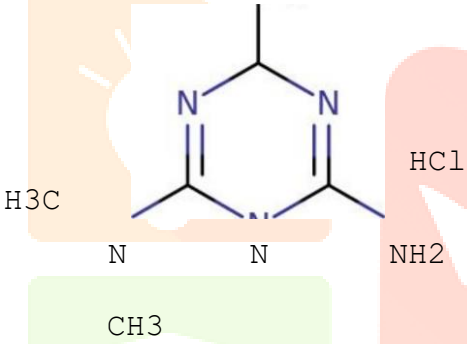


HISTORY OF IMEGLIMIN

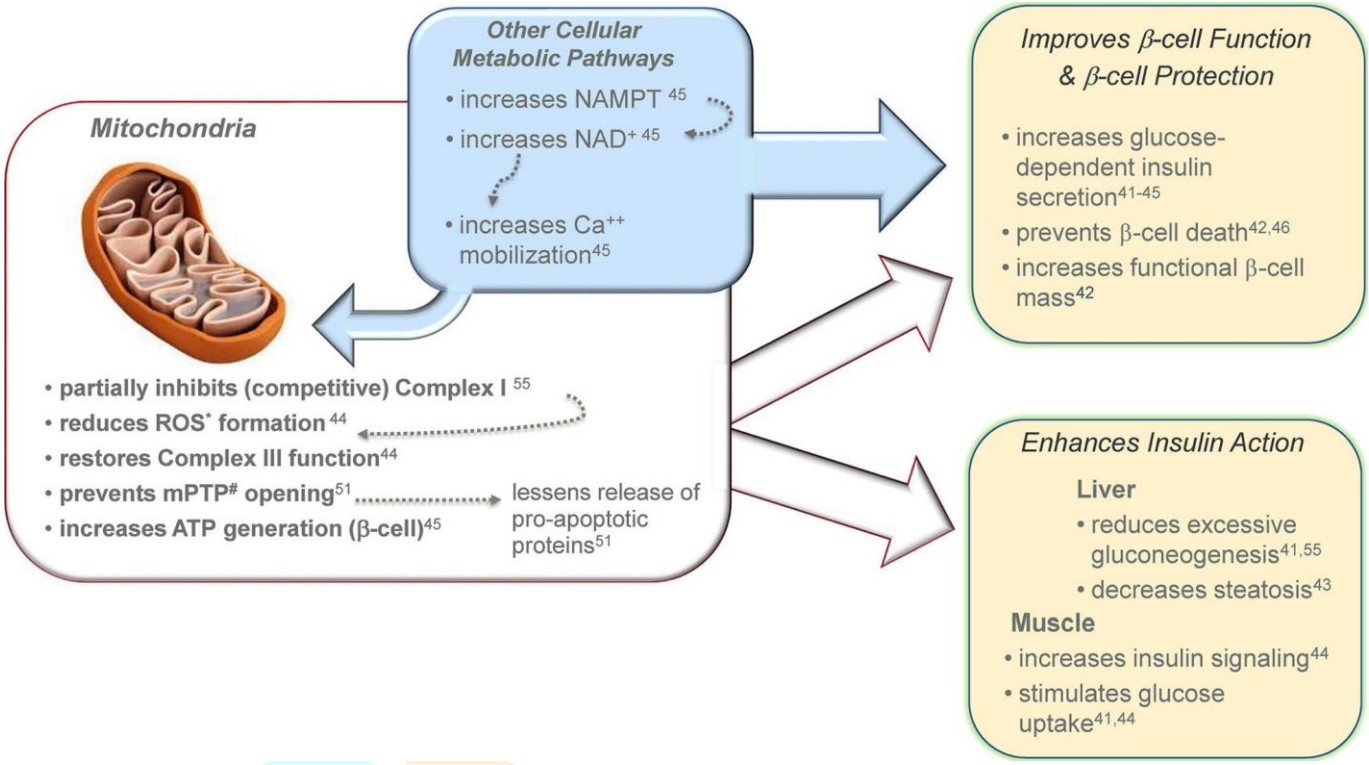
Imeglimin (EMD-387008,PXL-1501,brand name Twymeeg) is an oral anti-diabetic medication. It was approved for use in Japan june2021.1t is an oxidative phosphorylation blocker that acts to inhibit hepatic gluconeogenesis, increase muscle glucose uptake, and restore normal insulin secretion.

ENHANCED INSULIN ACTION

In the TIMES 1 phase Ill monotherapy trial , Imeglimin treatment for 24 weeks produced a significant effect on the Quantitative Insulin Sensitivity Check Index (QUICK), a measure of insulin sensitivity that correlates with result from glucose clamp studies. Specifically, mean QUICKI values were increased by 0.0093 in imeglimin versus placebo-treated patients(P=.005) after 24 weeks (Poxel, unpublished data). A similar effect on the related stumvoll index- an alternative calculated estimate of insulin sensitivity- was noted in an additional unpublished phase Il trial. Future studies are being planned to more directly measure the effect of Imeglimin on insulin sensitivity in humans.

MOLECULAR MECHANISM

Given the effects of Imeglimin on multiple organs and cell types, it is not surprising that effects related to mitochondrial dysfunction -which involves multiple tissues in T2Dmight underlie the pleiotropic beneficial phenotypic changes imparted by Imeglimin treatment. As depicted, there are several documented effects of Imeglimin leading to modulation of mitochondrial function and to potentially favourable downstream sequelea.



FUNCTION ON BETA CELLS

(Palaniappan Vinayagama,b, Vengojayparassad Senathipathic, Vishnu Shivamc,d,*, Nandhini Velraju. A Review. Diabetes Epidemiology and Management 12 (2023) 100164)

The aim of meta -analysis is to evaluate the role of imeglimin in glycemic control (HbAl c&FPG),Homeostatic model Assessment of beta-cell function, pro-insulin to cpeptide ration and its safety outcome in patients with type2 diabetes mellitus.

Method

A thorough literature search was performed on PubMed Central, PubMed, Cochrane, Wiley online library databases and efficacy outcomes such as changes in HbAl c, FPG, pro-insulin to c-peptide ratio and HOMA-b eta were summarized as standardized mean difference and safety outcomes were summarized as odds ratio. (PROSPERO registration no. CRD42023422787).

Results

Seven randomized controlled trials conducted on 1,454 patients with type 2 diabetes mellitus were included. Overall the random effects model meta-analysis of standardized mean difference demonstrated that Imeglimin was significantly associated with HbAlc reduction of-0.85% (95% CI-I .08 to-0.62, p

Diabetes and Alzheimer's disease common metabolic story

(Cristina Carvalhol and Paula I. Moreira. A Review science direct current opinion in neurobiology 2023, 79: 102694)

Type 2 diabetes and Alzheimer's disease two global epidemics that share several metabolic defect such as insulin resistance impaired glucose metabolism and mitochondrial defects. Type 2 diabetes (T2D) has attained the status of a global pandemic becoming one of major challengest to human health in 21 st century.

Mitochondria drug for diabetic kidney disease

(Akira Mima. A Review Heliyon 8 (2022) e08878) diabetes is the most common cause of chronic kidney disease and chronic hyperglycemia is a major cause of diabetic kidney disease. Diabetic kidney disease (DKD) is one of the most frequent causes of chronic kidney disease (CKD) in the United States. Chronic hyperglycemic conditions are thought to be the primary cause of DKD. However, it is clinically difficult to achieve glycemic control in individuals with diabetes. Recent advances in mitochondrial biology have provided a new understanding of mitochondrial dysfunction in DKD. Studies have revealed impaired mitochondria function in a variety of diabetic complications, including DKD moreover, abnormal mitochondrial f ission may be involved in the progression of DKD.
It has been reported that metformin or sodium-glucose cotransporter 2 (SGLT2) inhibitors may provide renal protection by improving mitochondrial dynamics and reducing oxidative stress. Thus, drugs that target the restoration of mitochondrial function may become novel therapeutic agents for DKD. Imeglimin is the first in a new class of oral antidiabetic drugs that can reduce reactive oxygen species production and increase mitochondrial DNA synthesis. This review outlines the potential thera peutic interventions that affect mitochondrial function and prevent DKD.

Imeglimin prevents heart failure

(Hiroki Kitakata, Jin Endo, Shun Hashimoto, Erika Mizuno, Hidenori Moriyama, Kohsuke Shirakawa, Shinichi Goto, Yoshinori Katsumata, Keiichi Fukuda, Motoaki Sano* A Review Biochemical and Biophysical Research Communications 572 (2021) 185e190)

Heart failure is a known negative prognostic factor in diabetic patient. Heart failure with preserved ejection fraction (HEPEF) which is heart failure with a left ventricular ejection fraction (IVEF)> 50%has emerged as an important clinical problem in patient with type2 diabetes mellitus (T2DM). The pathogenesis of heart failure with preserved ejection fraction (HFpEF) in obese diabetic patients has been implicated in meta inflammation. Increased expression of inducible nitric oxide synthase (iNOS) and dysfunction of the unfolded protein response (UPR), especially inositol-requiring enzyme laeX-box binding protein I (IRE la-Xbpls) signaling in the heart, have been associated with HFpEF. We investigated the effect of imeglimin, a potential new treatment for type 2 diabetes, on the pathogenesis of HFpEF. We induced obesity, impaired glucose tolerance, and cardiac hypertrophy with fibrosis, fat accumulation, and diastolic dysfunction in wild-type mice with a high-fat diet (HFD) and the nitric oxide synthase (NOS) inhibitor L-NAME for 16 weeks. Treatment with imeglimin starting at 10 weeks not only improved their abnormal systemic glucose metabolism and visceral obesity but also their cardiac ab normalities. We found that imeglimin suppressed the upregulation of iNOS, and restored the expression of Xbpls and the expression of the E3 ubiquitin ligase STIPI homology and U-box-containing protein I (STUB l), which is responsible for the degradation of Forehead box protein 01 (FoxOl), a direct transcriptional target of Xbpls.

Imeglimin profoundly affects the circadian clock in mouse embryonic fibroblasts

(Kotomi Miura a, Jun-ichi Morishige a, Jotaro Abe a, Pingping Xu a, Yifan Shi a, Zheng Jing a, Naoto Nagata a, Ryo Miyazaki b, Naoki Sakane c, Michihiro Mieda d, Masanori Ono e, Yoshiko Maida f, Tomoko Fujiwara g, Hiroshi Fujiwara h, Hitoshi Ando A Review Journal of Pharmacological Sciences 153 (2023) 215e220)

Imeglimin is a novel antidiabetic drug structurally related to metformin. Metformin has been shown to modulate the circadian clock in rat fibroblasts. Accordingly, in the present study, we aimed to determine whether imeglimin can impact the circadian oscillator in mouse embryonic fibroblasts (MEFs).the circadian clock primarily comprise a transcription translation -based autoregulatory feedback loop involving a set of clock genes and is known to almost all types of cells and synchronize behavior and physiology with 24-h environmental changes at both systemic and cellular levels.

Methods

MEFs carrying a Bmall -Emerald luciferase (Bmal I-ELuc) reporter were exposed to imeglimin (0.1 or 1 mM), metformin (0.1 or I mM), a nicotinamide phosphoribosyltransferase inhibitor FK866, and/ or vehicle. Subsequently, BmallELuc expression and clock gene mRNA expression levels were measured at 10-min intervals for 55 h and 4-h intervals for 32 h, respectively.

Results

Imeglimin significantly prolonged the period (from 26.3 to 30.0 h at 0. I mM) and dose dependently increased the amplitude (9.6-fold at I mM) of the Bmall-ELuc expression rhythm; how ever, metformin exhibited minimal effects on these parameters. Moreover, imeglimin notably impacted the rhythmic mRNA expression of clock genes (Bmall, Perl, and Cry l). The concurrent addition of FK866 partly inhibited the effects of imeglimin on both Bmall -ELuc expression and clock gene mRNA expression.

Anti — diabetic effects of astaxanthin -rich extract derived from paracoccus carotinifaciens on pancereatic beta cells

(Hikari Hirakida a , Shinsuke Nakamura Masamitsu Shimazawa a , c a , * , Hideaki Hara , Satoshi Inagaki a , a c a , Shohei Tsuji Masahiro Hayashi A Review Journal of Functional Foods 97 (2022) 105252)

Astaxanthin is a natural pigment that is used as a dietary supplement. Many experiments have shown that astaxanthin has positive effects against various diseases including diabetes. Adonixanthin and adonirubin are biosynthetic intermediates of ßcarotene to astaxanthin and possess the same radical scavenging activity as astaxanthin. In this study, we evaluated the antidiabetic effect on pancreatic ß cells of astaxanthin-rich extract (ARE) derived from Paracoccus carotinifaciens, which contains several carotenoids such as astaxanthin, adonir ubin, and adonixanthin. Specifically, we studied the effects on insulin secretion and cytoprotection as well as on intracellular reactive oxygen species (ROS) generation and mitochondrial superoxide production.

Therapeutic strategy of biological macromolecules based natural bioactive compounds of diabetes mellitus and future perspectives

Naiyer Shahzad Imran Shahid a a , * , Abdullah R. Alzahrani , Ibrahim M. Alanazi a a , Ibrahim Abdel Aziz Ibrahim , Alaa Hisham Falemban Mohammad Tarique Imam b , Nehal Mohsin c a , , Mohd Fahami Nur Azlina d a , , Palanisamy Arulselvan A review Heliyon 10 (2024) e24207

High blood glucose levels are a hallmark of the metabolic syndrome known as diabetes mellitus. More than 600 million people will have diabetes by 2045 as the global prevalence of the disease continues to rise. Contemporary antidiabetic drugs reduce hyperglycemia and its consequences.

However, these drugs come with undesirable side effects, so it's encouraging that research into plant extracts and bioactive substances with antidiabetic characteristics is on the rise. Natural remedies are preferable to conventional anti-diabetic drugs since they are safer for the body, more affordable and have fewer potential adverse effects. . Biological macromolecules such as liposomes, niosomes, polymeric nanoparticles, solid lipid nanoparticles, nanoemulsions and metallic nano particles are explored in this review. Current drug restrictions have been addressed, and the effectiveness of plantbased antidiabetic therapies has enhanced the merits of these methods. Plant extracts' loading capacity and the carriers' stability are the primary obstacles in developing plant -based nanocarriers. Hydrophilic, hydrophobic, and amphiphilic drugs are covered, and a brief overview of the amphipathic features of liposomes, phospholipids, and lipid nanocarriers is provided. Metallic nanoparticles' benefits and attendant risks are highlighted to emphasize their efficiency in treating hyperglycemia. Diabetes mellitus (DM) is a recent epidemic that may be traced back to genetic and environmental changes [l]. Modern lifestyles Diabetes mellitus (DM) is a recent epidemic that may be traced back to genetic and environmental changes .

Imeglimin prevents visceral hypersensitivity and colonic hyperpermeability in irritable bowel syndrome rat model

Tsukasa nozu ,saori miyagishi ,masatomo ishioh ,kaoru takakusaki, toshikatsu Okumura, A review journal of pharmacological sciences 153(2023)26-30

Visceral hypersensitivity and leaky gut, which are mediated via corticotropin-releasing factor (CRF) and Toll-like receptor 4 are key pathophysiology of irritable bowel syndrome (IBS). Metformin was reported to improve these gastrointestinal (GI) changes. In this study, we attempted to determine the effects of imeglimin, which was synthesized from metformin on GI function in IBS rat models. Imeglimin blocked lipopolysaccharide- or CRF-induced visceral hypersensitivity and colonic hyperpermeability. These ef

fects were prevented by compound C or naloxone. These results suggest that imeglimin may be effective for the treatment of IBS by improved visceral sensation and colonic barrier via AMPK and opioid receptor.

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