



Pharmacotherapy in Endocrinology: Diabetes, Obesity, and Hyperlipidemia- Review Article

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Abstract

The field of endocrine pharmacology is very wide but most of studies in the recent years from the world and Iran have focused on diabetes, osteoporosis, and lipid disorders. In the present review, we tried to evaluate the improvements and publications in that field briefly. Interestingly, many of studies have focused on agents that have traditional and natural origin. Although few basic studies have gone on the direct line to complete preclinical and some clinical trial studies, there are many non-clinical studies that have proved efficacy of many compounds in endocrine diseases but these studies were not continued at clinical stages to reach a drug. However, it is appreciable that, some researchers have given novel ideas that deserve investment by grant bodies to reach out valuable works. We believe that science of endocrine pharmacology is still young and more quality studies are still needed to introduce effective medications for diseases like diabetes and osteoporosis or even obesity and lipid disorders.

Keywords: Pharmacotherapy, Diabetes, Osteoporosis, Lipid disorders, Emerging therapies

Introduction

The field of endocrine pharmacology is very wide and includes many organs and many disorders but most of studies in the recent years from the world and Iran have focused on diabetes, osteoporosis, and lipid disorders. In the present review, we tried to evaluate the improvements and publications in that field briefly. Hopefully, in the recent years, many efforts were performed to explore pathogenesis, mechanism of disease, and pharmaceutical management of endocrine diseases. Many of studies focused on agents that have had traditional and natural origin. Studies in this field have been promising in exploring the role of oxidative stress in two major human endocrine problems including diabetes and osteoporosis. In this respect, new

drug form herbal source named Semelil (Angipars) is now available for management of diabetic foot ulcer a major consequence of advanced human diabetes. In the present review, most of these studies were described in brief but our recommendation to readers of this review is to follow the cited papers to improve their understanding.

Diabetes Mellitus

In diabetes mellitus, major studies were done on anti-hyperglycemic, antihyperlipidemic and antioxidant effects of various medicinal plants and synthetic drugs. Fundamental studies have been done to clarify pathogenesis and consequences of diabetes in an attempt to introduce better pharma-

ceutical agents in this widespread disease of the world. Animal studies, clinical trials and systematic reviews have been done in this area.

Herbal Medicines

Animal studies

The mechanism of action of walnut (the seed of *Juglans regia*) leaf and ridge on hepatic glucose metabolism in diabetic mice was explored. Experimental diabetes was induced in mice by single intravenous administration of streptozotocin (STZ, 60 mg/kg). Isolated extracts from walnut leaf and ridges were administered in a single dose of 400 mg/kg orally. Treatment by both leaf and ridge extracts improved blood glucose level and decreased liver phosphoenol pyruvate carboxykinase activity, the key enzyme for gluconeogenesis, and increased blood insulin levels. Authors concluded that Walnut decreases blood glucose via inhibition of hepatic gluconeogenesis and increasing pancreatic insulin secretion (1).

Immunomodulatory, antioxidative, and anti-inflammatory effects of *Silybum marianum* seed extract (silymarin) on STZ-induced type 1 diabetes mellitus mouse was studied. Different doses of silymarin (20, 40, and 80 mg/kg) were used in that experiment. Results indicated that Silymarin reduces levels of inflammatory cytokines and oxidative stress mediators of pancreatic tissue in an almost dose-dependent manner. Silymarin seems to be helpful in type 1 diabetes mellitus but its benefit in human type 1 diabetes mellitus remains to be elucidated by clinical trials (2).

Significant wound healing effect of electromagnetically-processed *Melilotus officinalis* extract (MAE) was reported in diabetic mice. The study showed that MAE accelerates wound closure and interestingly improves the quality of wound tissue with an efficient hair growth on the scars. Electromagnetic processing of MAE showed an excellent efficacy on diabetic ulcer in mice (3).

Treatment of STZ-induced diabetic rats with aerial parts of *Phlomis anisodonta* methanolic extract (PAE), showed significant reduction in fasting blood glucose, and an increase in serum insulin levels. PAE also protected rats from STZ-induced

weight loss and activated the hepatic antioxidant enzymes (4).

Considering reported antidiabetic effects of *Satureja khuzestanica* essential oil (SKEO), effects of SKEO on rat hepatic key enzymes of gluconeogenesis and glucogenolysis has been explored. Besides increasing glucogenolysis, SKEO decreased gluconeogenesis which may be the responsible mechanism of its antihyperglycemic effects through depleting hepatic glycogen storage (5).

Semelil (ANGIPARS™), a novel herbal-based compound containing *Melilotus officinalis* extract, has been formulated for treatment of chronic wounds, specially diabetic foot ulcer. Toxicologic, pharmacologic, and pathomorphologic effects of intramuscular and intraperitoneal injections of Semelil in mice and Wistar rats were explored. In acute toxicity study, its LD₅₀ was determined. Adverse effects of drug at doses close to LD₅₀ included a depressed mood, narcosis and sleepiness. No adverse pharmacological or toxicological effects were reported in single dose or daily administration of the diluted drug (6).

Daily intramuscular administration of Semelil in dogs during one month study period did not have any adverse health or toxicity effects. There were no alterations in main organs' function (7).

As part of the safety evaluation process, potential genotoxicity of Semelil was assessed in three different in vitro and in vivo tests, including bacterial reverse mutation (Ames test), mammalian bone marrow chromosomal aberration, and rodent dominant lethal assays. Semelil had negative effects at different doses in the Ames test. Levels of chromosomal aberrations in bone marrow cells of mice had no significant differences between experimental and control group.

The number of lethal mutations in germ cells of male mice following a single dose administration of Semelil and rate of post-implantation losses did not increase significantly as compared to control group (8). These studies revealed a favorable safety profile for the product.

Human studies

After conducting phase 1 and 2 clinical trial of Semelil (ANGIPARS™) in patients with diabetic

foot ulcer, in a multicenter clinical study, intravenous administration of Semelil ended to a significantly greater wound closure (9-11). Further studies on oral and topical route of administration showed promising results and increased the incidence of complete wound closure (12).

Oral administration of Semelil in patients with type 2 diabetes did not have any significant effect on oxidative stress status. It seems that mechanisms other than antioxidative effects are responsible for the beneficial effects of Semelil in treatment of diabetic foot ulcers (13).

Treatment of type 2 diabetic patients by dried leaves of *Satureja khuzestanica* improved total cholesterol, LDL-cholesterol and HDL-c and total antioxidant power of plasma, but it did not alter blood glucose or triglyceride levels. *Satureja khuzestanica* can be recommended as a supplement in patients with type 2 diabetes and hyperlipidemia (14).

Reviews

Medicinal plants which grow and have history of traditional medicine in Iran and shown antioxidative properties in animal or human studies have been reviewed. Animal studies revealed that *Ferula szovitsiana*, *Nigella sativa*, *Rosa damascena* petal, *Phlomis anisodonta*, *Rosemary*, *Zataria multiflora* Boiss, *Saffron*, *Amirkabiria odoratissima* mozaffarian, *Ficus carica* Linn., *Ziziphora clinopoides*, *Carica papaya*, *Chichorium intybus*, *Turmer*, *eugenol*, *Curcumin*, and *Pistacia vera* L may reduce lipid peroxidation. In human studies *Cinnamomum zeylanicum* and *Echium amoenum* Fisch and C.A. reduced lipid peroxidation and improved total anti oxidant power in healthy volunteers. Antihyperlipidemic effects were shown by *Silybum marianum*, wheat germ, and garlic (15).

Safety and efficacy of *Teucrium* species in different animal and human conditions have been reviewed. Hypoglycemic effects of *Teucrium* have been reported in some animal and one human study. The responsible mechanism for its anti-diabetic effects seems enhancement of insulin secretion from pancreas. Decrease in serum cholesterol and triglyceride has been reported in one animal study. Antispasmodic, antinociceptive, antioxidan-

tive and antiinflammatory properties of *Teucrium* are other beneficial effects that have been shown in studies. Regarding safety issues, long term or high dose administration of *Teucrium* may cause progressive impairment of neuromuscular coordination and hepatic damage (16).

Iranian medicinal plants with antidiabetic effects in animal or human studies have been reviewed. In human studies, treatment with *Citrullus colocynthus* L, *Silybum marianum*, *Psyllium*, *Teucrium polium*, and *Pomegranate* showed significant decrease in blood glucose. Medicinal plants that showed significant blood glucose lowering effects in animal studies were *Walnut leaf*, *Coriander*, *Pomegranate*, *garlic*, *Satureja khuzestanica*, *Phlomis anisodonta*, *Trigonella foenumgraecum*, *Olive (Olea europaea L)*, *Capsicum frutescens*, *Achillea santolina*, *Aloe vera*, *Salvia officinalis*, *Anathum graveolens*, *Teucrium polium*, *Urticadioica*, *Morus nigra*, *Morus alba*, *salvia lenifoliabenth leaf* and *Cynara scolymus* (17).

Since the therapeutic values of the genus *Satureja* L. is well recognized, existing scientific data about this genus has been reviewed. Based on current evidences, antibacterial, antifungal, antiviral, analgesic, vasodilatory, antioxidative and antidiabetic activities are defined as the most applicable properties of *Satureja* subspecies. The valuable therapeutic effects of this genus are mostly related to essential oil, flavonoid and triterpenoid contents. Combination of two or more subspecies acting by different mechanisms may produce synergistic effects and should be considered (18,19).

Phosphodiesterase inhibitors (PDEIs) are a class of drugs with various pharmacological properties such as cardiostimulant, vasodilator, smooth muscle relaxant, antithrombotic, bronchodilator, antiinflammatory, antidepressant and cognitive function enhancer. Some pharmacologically active substances with herbal origin showing PDEI activity mainly belong to alkaloids, flavonoids, and saponins. So, studies on herbal PDEIs were reviewed and their therapeutic applications were evaluated. Reviewed studies were mainly in vitro and thus for more conclusive results in vivo and human studies are required. Screening plants with PDE inhibitory activity may help to develop phytotherapeutic prod-

ucts or find new lead structures with PDEI pharmacological activity (20).

Synthetic drugs

Animal studies

It has been suggested that increased oxidative stress involves in the pathogenesis and progression of diabetic tissue damage. Treatment of STZ-induced diabetic rats by different PDEIs (milrinone, sildenafil, theophylline) reduced lipid peroxidation and increased total antioxidant capacity. The antioxidative activities of these agents may be attributed to their enhancing effects on cellular cyclic nucleotides (21).

Effects of short-term administration of sildenafil, a selective PDEI, on serum glucose and hepatic glycogenolysis and gluconeogenesis in rats have been studied. High dose of sildenafil significantly decreased serum glucose levels. While hepatic gluconeogenesis remained unchanged, hepatic glycogenolysis reduced. This effect of sildenafil seems to be related to its nitric oxide (NO) mimicking activity and antioxidative properties (22).

Human studies

Alterations in lipid peroxidation level, antioxidative power, and concentrations of epidermal growth factor (EGF) and NO in saliva and blood of patients with type 1 diabetes in comparison to healthy volunteers has been studied. Increased total antioxidant power in the presence of normal lipid peroxidation in plasma and saliva of patients with type 1 diabetes was detected. EGF was increased in saliva but it was reduced in plasma. NO levels increased in both saliva and plasma of patients with type 1 diabetes (23).

Although, carvedilol had shown antioxidative properties, short term administration of carvedilol in patients with type 2 diabetes had no significant effects on oxidative stress status, fasting blood sugar and hemoglobin A1c (24).

Administration of pentoxifyllin 400 mg four times a day in patients with type 2 diabetes reduced lipid peroxidation in plasma but it did not have any significant effect on total antioxidant power, and plasma levels of EGF and NO (25).

Efficacy of atorvastatin (10 mg), simvastatin (20 mg) and lovastatin (20 mg), once daily on lipid profile of patients with type 2 diabetes was compared over a 12 week study period. After treatment differences in high density lipoprotein cholesterol (HDL-c) were not statistically significant between three groups. Low density lipoprotein cholesterol (LDL-c) levels were significantly lower in atorvastatin group compared with the simvastatin group after treatment. The study confirmed that atorvastatin is a better choice among statins for the management of hyperlipidemia in patients with type 2 diabetes (26).

Considering the long half-life of atorvastatin, efficacy of alternate-day versus once-daily dosing regimens of atorvastatin in reduction of LDL-c in Type 2 diabetic patients has been studied. Reduction of LDL-c in once daily administration of atorvastatin was significantly different as compared to alternate day regimen (36% vs. 28%). Patients who met the LDL-c goals were more than two times in once daily rather than alternate day regimen (68% vs. 33%). This study showed that daily regimen is more effective than alternate regimen in reducing LDL-c (27).

Reviews

Enhanced production of reactive oxygen substances (ROS) and disturbed capacity of antioxidant defense in patients with diabetes has been reviewed. The role of oxidative stress in development of diabetes complications has been discussed. Reports on effects of different antioxidants in the management of diabetes have been reviewed. Finally the review indicated that oxidative stress is involved in pathogenesis of diabetes and its complications. Antioxidants may reduce oxidative stress and reduce diabetes complications (28). Islet transplantation is a promising treatment for type 1 diabetes. Since oxidative stress plays an essential role in cell injury during islet isolation and transplantation process, the role of antioxidants in this procedure has been reviewed. Almost all the antioxidants which were used in the invitro studies improved islet viability and insulin secretion. The major outcome of antioxidant therapy in all invivo studies was enhanced blood glucose

control following transplantation. Antioxidants also improved islet transplantation procedure. Although there is no sufficient evidence to come to definite conclusions about the efficacy of supplements, the benefits of antioxidants in islet isolation procedure should be considered (29).

Targets and new therapies

Since existing treatments for diabetes have some limitations regarding their side effects (particularly weight gain and hypoglycemia) and contraindications, there is need for new therapies. Based on basic and clinical studies new treatment targets have become available that we are going to mention some of them in this part:

Sodium glucose transporter-2 (SGLT-2) inhibitors

Glucose reabsorbs from the glomerular filtrate in the renal proximal tubule via SGLT-2. Inhibitors of this transporter block renal glucose reabsorption, promote urinary glucose excretion. Increased urinary glucose lost lowers hyperglycemia but hypoglycemia has not been reported with these agents yet. Since patients loose calorie by glucosuria, these agents may cause weight loss. Sergliflozin and dapagliflozin belong to this class of drugs (30). Efficacy and safety of dapagliflozin in patients with type 2 diabetes who had inadequate glycemic control with metformin (≥ 1500 mg daily) was assessed. In this phase 3 multicenter, double-blind, placebo- controlled trial, at week 24 HgA_{1c} reduced by 0.30% in the placebo group, compared with 0.67%, 0.7% and 0.84% in dapagliflozin 2.5 mg, 5 mg, 10 mg groups, respectively. Incidence of hypoglycemia was similar in the dapagliflozin and placebo groups. Signs, symptoms, and other reports suggestive of genital infections in dapagliflozin groups were more frequent than placebo group (31).

Glucokinase activators

Glucokinase is a glucose- sensing enzyme located in liver and pancreas. Activation of this enzyme boosts hepatic glucose uptake and insulin secretion from pancreas. Selective activators of glucokinase are currently under development.

Sirtuins

Sirtuins are enzymes that are associated with many diseases related to advancing age, such as atherosclerosis and type 2 diabetes mellitus. Increased sirtuin expression improves β -cell function and insulin release. Resveratrol, found in grapes and red wine is a natural sirtuin activator.

Glucagon receptor antagonists

Glucagon increases hepatic glucose output and blood glucose level accordingly. High levels of glucagon have been reported in patients with type 2 diabetes. Antagonists of glucagon receptor are other therapeutic targets that a number of them have been identified (31).

11-beta-hydroxysteroid dehydrogenase type 1 inhibitors

11Beta-hydroxysteroid dehydrogenase type 1 enzyme (11-beta-HSD1) catalyzes glucocorticoid activation in metabolic tissues (e.g. liver, skeletal muscle and adipose tissue).

It is strongly involved in the pathogenesis of obesity, type 2 diabetes mellitus and metabolic syndrome. Selective 11-beta-HSD1 inhibitors reduce local glucocorticoid and improve insulin sensitivity, glucose tolerance and lipid profile. Currently clinical trials of these agents are undergoing (32).

Selective peroxisome proliferator-activated receptor gamma (PPAR gamma) modulators

Full agonists of PPAR gamma have shown acceptable glucose lowering activity in patients with type 2 diabetes mellitus.

These agents do not have some of the adverse effects such as hypoglycemia and gastrointestinal discomfort that are associated with some other medications used to treat diabetes.

However they have safety and tolerability issues such as weight gain, edema, congestive heart failure and bone fracture. Selective modulation of PPAR gamma provides the opportunity to improve the safety profile while retaining the desirable therapeutic effects. These agents are being tested clinically (33, 34).

New therapies for diabetes

Many patients with type 2 diabetes are obese (diabetes) and numerous antidiabetes medications are associated with weight gain. Therefore, treatment of diabetes is challenging. Newer pharmacotherapies offer a new option to reduce hyperglycemia and facilitate weight loss or being weight neutral. The glucagon-like peptide-1 (GLP-1) receptor agonists, amylinomimetics and sodium-glucose cotransporter2 inhibitors promote weight loss. The dipeptidyl peptidase-4 (DPP-4) inhibitors are weight neutral. Selective modulators of PPAR gamma mitigate effects leading to adiposity and fluid retention (35, 36).

Obesity

Obesity has emerged as one of the principle worldwide health problems in industrialized countries. It is associated with many diseases, particularly diabetes, dyslipidemia and hypertension. On the other side there are still alarming unmet clinical need for safe and effective therapies to overcome this issue. In this part anti-obesity targets and therapies will be reviewed.

Original studies

L185008F, a synergistic composition of *Moringa oleifera*, *Murraya koenigi*, and *Curcuma longa*, has been studied in diet-induced obese rats. This compound inhibits preadipocyte differentiation and potentiates lipid breakdown in mature adipocytes. L185008F significantly reduced weight gain and further toxicology studies demonstrated the broad spectrum safety of L185008F in animal studies (37).

Cevoglitazar belongs to the dual agonists of peroxisome proliferator-activated receptor (PPAR)-alpha and gamma subtypes which are as a developing therapeutic approach for treatment of type 2 diabetes mellitus and diabetic dyslipidemia. Effects of Cevoglitazar on energy homeostasis in two animal models of obesity have been explored. Results revealed that Cevoglitazar has unique beneficial effect on energy balance in addition to glycemic control and improvement of metabolic indices (38).

Oxyntomodulin (Oxm) is a hormone which has demonstrated beneficial effects for ameliorating diabetes. This hormone has short half-life due to degradation by dipeptidyl peptidase-IV enzyme. In-vivo effects of enzyme resistant analogues of Oxm were examined in obese diabetic (ob/ob) mice. Their ability to improve glucose homeostasis, insulin secretion and satiety was reported (39).

Interaction between long-term adiposity signals (e.g., Leptin), and short-term satiation signals (e.g., amylin) is a part of neurohormonal control of body weight. In animal studies amylin/Leptin combination treatment have had shown notable, synergistic, fat-specific weight loss. Following the animal studies, efficacy of combined amylin/leptin agonist (with pramlintide/metreleptin) had studied in obese or overweight subjects in a randomized controlled trial. Results were promising and they support development of this combination as a novel therapeutic approach for obesity (40).

In order to evaluate efficacy of combination agents targeted at a specific obesity regulatory pathway, effects of pramlintide alone or in combination with either phentermine or sibutramine has been explored. In this study weight reduction at week 24 with either combination treatment was greater than with pramlintide alone or placebo. The study supports the potential of pramlintide-containing combination treatments for obesity (41). Hypothalamic melanocortin system and the mesolimbic reward system are two key CNS pathways w regulating food intake and body weight. Combination of sustained-release naltrexone and bupropion was developed to stimulate hypothalamic proopiomelanocortin neurons with bupropion while simultaneously blocking opioid-mediated proopiomelanocortin autoinhibition with naltrexone. Additionally, the preclinical data together with pharmacology and therapeutic applications for naltrexone and bupropion in addictive disorders, indicates that synergism of these drugs in midbrain dopamine areas reduces food intake. Suggesting mechanism of action of this combination might also be modulation of mesolimbic reward pathways.

The Contrave Obesity Research 1 (COR-1) study was a 56-week trial that assessed the efficacy, safe-

ty, and tolerability of this combination over 1 year in overweight and obese participants. Mean body weight reduction in placebo group was 1.3% comparing to 6.1% and 5% in naltrexone 32 mg plus bupropion and naltrexone 16 mg plus bupropion respectively. The most common adverse effect of the combination was nausea. Results indicated that it could be considered as a new therapeutic option for obesity (42).

Reviews

Efficacy and safety of herbal medicines in treatment of obesity in animal and human studies has been reviewed by Hasani-Ranjbar et al. (2009). This review indicates that *Cissus quadrangularis* (CQ), *Sambucus nigra*, *Asparagus officinalis*, *Garcinia atroviridis*, ephedra and caffeine, Slimax (extract of several plants including *Zingiber officinale* and *Bofutsushosan*) have shown a significant weight reduction effects in studies. Regarding the safety issues, no significant adverse effects or mortality were reported excepting ephedra, caffeine and *Bofutsushosan*. Finally, supplements containing ephedra, CQ, ginseng, bitter melon, and zingiber were proposed as candidates for effective management of obesity (43).

Scientific data of natural products with anti-obesity effects have been reviewed by Yun. In this review products are categorized according their mechanism of action into five groups including: lipase inhibitory effect, suppressive effect on food intake, stimulating effect on energy expenditure, inhibitory effect on adipocyte differentiation, and regulatory effect on lipid metabolism (44).

Meta-analysis of eight trials on efficacy of orlistat and sibutramine on obesity and cardiovascular risk factors in obese adolescents has been done. The mean weight loss between intervention and control groups after a minimum follow up of 6 months was 5.25 kg. There was little evidence to suggest that treatment with sibutramine is associated with small increase in blood pressure (45).

Targets and new therapies

Despite the increasing use of prescription weight loss medications, the history of medical management of obesity is no great success story because

many anti-obesity drugs, including fenfluramine-phentermine, were withdrawn by the US Food and Drug Administration (FDA) because of serious adverse reactions.

At present, only orlistat and sibutramine have been approved for long-term use by the FDA. However, sibutramine was withdrawn from the market in 2010 due to concerns that it could lead to an increased risk of developing stroke and myocardial infarction. Rimonabant was approved in the European Union in 2006 but officially withdrawn in 2009 by the European Medicines Agency. For these reasons, new treatments for obesity with improved safety profile and efficacy are urgently needed. There are still many compounds in preclinical or early clinical development stages which some of them reviewed in this part.

Novel peripheral targets

Glucagon like peptide-1 (GLP-1)

GLP-1 is an incretin hormone which enhances insulin secretion. Animal studies initially identified a reduction in food intake after administration of GLP-1 and subsequently a similar effect was recognized in patients with type-2 diabetes following infusion with GLP-1. Satiety inducing properties of GLP-1 has made it as prime target for management of diabetes and obesity. However GLP-1 has short half- life due to rapid deactivation by DPP-4 and is not suitable to use as a drug. Exenatide is the first GLP-1 agonist that is resistant to DPP-4 degradation. Phase III clinical trials of exenatide in patients with type 2 diabetes showed not only improvement in glycemic control but also significant reduction in body weight (46). Recent data has suggested that combined GLP-1 and glucagon receptor agonism may have superior efficacy in inducing satiety and body weight reduction (47).

Oxyntomodulin

Oxyntomodulin, secreted by intestinal L-cells, is released during food ingestion. It is known to inhibit gastric acid secretion and delay gastric emptying. In rodent studies oxyntomodulin reduced food intake, increased energy expenditure and reduced the rate of increase in body weight. In a

four week trial of oxyntomodulin in obese volunteers, weight loss was 1.8 kg greater than that was achieved by placebo. Subsequently it was identified that oxyntomodulin administration was associated with increased energy expenditure in addition to satiety induction (47,48).

Peptide YY

Peptide YY (Peptide tyrosine tyrosine) is another product of intestinal L-cells, is co-secreted with GLP-1 and oxyntomodulin after meals. The hormone exists in two major forms in circulation:

PYY₁₋₃₆ and the predominant circulating moiety PYY₃₋₃₆. Initial preclinical studies in rodents indicated anorectic and weight loss inducing effects of PYY₃₋₃₆. However these studies were questioned by other research groups who were unable to replicate the results. Infusion of PYY₃₋₃₆ in normal weight and obese humans reduced food intake. No long term trials of the effectiveness of this substance have been published, but it has attracted considerable interest as an anti-obesity target. Initial attempts to develop intranasal delivery of PYY₃₋₃₆ after significant problems with nausea and vomiting was halted (47, 48).

Cholecystokinin

Cholecystokinin (CCK) is released by endocrine I-cells in the small intestine after food ingestion. Peripheral administration of CCK causes early meal termination in rats. However in a clinical trial of a CCK1 receptor agonist developed by GlaxoSmithKline, mean body weight in placebo and treatment group was similar after 24 weeks study (47,48).

Amylin

Amylin is co-secreted with insulin by pancreatic islet β -cells. In animal studies peripheral administration of amylin in rats retarded gastric emptying and reduced food intake. Pramlintide is a stable analogue of amylin which has FDA approval for use as an adjunct to insulin treatment in both type 1 and type 2 diabetes mellitus and its use in these patients have been associated with modest weight reduction. In a clinical trial comparing effects of several doses of pramlintide in non-

diabetic obese individuals, progressive weight reductions were observed at 12 months. The placebo corrected weight loss for 120 μ g and 360 μ g was 6.1 kg and 7.2 kg respectively (47,48).

Ghrelin

In contrast to other gut hormones, it is a potent orexigenic agent. Current data suggest that ghrelin antagonists, or inverse agonists might be effective in management of obesity (47,48).

Novel central targets

Monoamine reuptake inhibitors

Monoamine regulation of food intake and energy balance is a great field of interest and offers various opportunities for pharmacological intervention. These opportunities vary from nonspecific strengthening signaling pathways such as triple reuptake inhibitors to targeting specific subtypes of monoamine receptors (e.g. 5-HT_{2c} and 5-HT₆) (48).

Cannabinoid antagonists

There is a large body of evidence that indicates endocannabinoids increase food intake via CB₁ receptor. Rimonabant is a CB₁ antagonist which progressed to phase III trials but due to significant increase in psychiatric adverse events, the FDA refused marketing authorization. Subsequently in 2008, the EMA withdrew its authorization for rimonabant in Europe. This side effect is considered as class issue for first generation CB₁ antagonists. Under investigation approaches to overcome this issue includes non-brain penetrant CB₁ antagonists and neutral CB₁ antagonists (47).

Direct modulation of hypothalamic neuropeptide transmitters

A number of hypothalamic neuropeptide transmitters have either orexigenic or anorexigenic effects. Manipulation of these targets offers another pharmacological opportunity to regulate food intake.

Neuropeptide Y antagonists

NPY is a widely distributed neurotransmitter within the brain. NPY was detected as a potent

central orexigen in the 1980s. A number of evidence indicates that the Y1 and Y5 receptors are critical to the effects of NPY on feeding behavior. Selective NPY antagonists, particularly targeting NPY₅ receptors inhibited feeding and reduced body weight in models of obesity (47,48).

Melanocortin MC₄ receptor agonists

Decreased activity of melanocortin system is associated with hunger and stimulation of feeding. Injections of MC₄ agonists have shown to decrease food intake. Selective agonists of MC₄ have been considered as potential treatments for obesity. However lack of suitable nonpeptide agonist ligands and concerns about cardiovascular safety issues have limited clinical development of this target (47, 48).

Melanin concentrating hormone antagonists

MCH is an orexigenic peptide which affects food intake and body weight. MCH is expressed in the lateral hypothalamus in response to energy restriction and leptin deficiency. Much effort is currently being committed to develop novel MCH1 receptor antagonists. Although few have entered clinical trials to day (47, 48).

Hyperlipidemia

Targets and new therapies

Investigations have shown that patients who are high risk for cardiovascular events, more often fail to accomplish their treatment goals. Some patients with high baseline low density lipoprotein cholesterol (LDL-c) levels require larger reductions that may not achieve with current treatments. Although large clinical trials indicate that reduction of LDL-c with statins, which are the mainstays of lipid lowering therapy, reduces major cardiovascular events, still considerable residual risk remains. Currently new targets for treatment of dyslipidemia have attracted a great concern to achieve more effective reductions in cardiovascular morbidity and mortality. The main pathways which are targeted as new therapeutic options are regulation of lipoprotein assembly, lipoprotein clearance, and pro-atherogenic lipoprotein modification.

Inhibition of lipoprotein assembly ***Microsomal transfer protein inhibition***

Microsomal triglyceride transfer protein (MTP) transfers neutral lipids (e.g. Triglycerides, phospholipids, cholesterol ester) to apoB which is rate limiting step in synthesis of chylomicron and VLDL. Systemic MTP inhibition affects both intestine and liver and reduces LDL-c up to 50% by significant decrease in apoB production. However clinical trials were not promising due to unacceptable gastrointestinal and hepatic side effects. Besides decrease in apoA1 and HDL-c were reported. Restraining the inhibition of MTP to intestine might eliminate hepatic side effects. Such inhibitors are currently under clinical investigations (49).

Antisense oligonucleotides and small interfering RNA targeting apoB

Antisense oligonucleotides (ASO) and interfering RNA (RNAi) induce their target's mRNA destruction and inhibit protein production. In a clinical trial with an ASO, Mipomerson, a dose dependent effect on circulating apoB and LDL-c was observed. Mipomerson is currently in phase III clinical development. RNAi are more novel and they have shown to reduce apoB synthesis and LDL-c in animal studies (49).

Enhancement of lipoprotein clearance

Proprotein convertase subtilisin kexin type 9 inhibition

Proprotein convertase subtilisin kexin type 9 (PCSK9) is a proteinase that regulates intracellular cholesterol via alteration of LDL receptor activity. PCSK9 binds to the LDL receptor which is located on the surface of hepatocytes and impairs its internalization and recycling to the cell surface. PCSK9 stimulates LDL receptor degradation by lysosomes (50).

The hypothesis that inhibiting PCSK9 might lower LDL-c has been proved by early studies in subjects with loss of function mutations and confirmed in animal models. Several strategies might be tested to inhibit PCSK9, inhibiting its synthesis or targeting its interaction with the LDL-r (49).

Thyroid hormone analogues

Thyroid hormone is necessary for optimal activity of the LDL receptor. Increased levels of thyroid hormone, especially triiodothyronine (T₃) is associated with lower LDL-c but also unwanted effects on heart and bones. T₃ decreases LDL-c by increasing lipoprotein lipase activity and LDL clearance. There are two major thyroid hormone receptors (α and β) and several isoforms. TR- α plays a major role in the heart, while TR- β is highly expressed in the liver and controls blood cholesterol level. Some selective TR- β agonists have been developed and studied, but results were not promising. Recently, there is some renewed interest in TR specific analogues to improve lipid profile without expressing adverse cardiac effects (49, 50).

Inhibition of pro-atherogenic lipoprotein remodeling

Cholesterol ester transfer protein inhibitors

Cholesteryl ester transfer protein (CETP) contributes to an atherogenic lipoprotein profile by redistributing cholesteryl esters from high density lipoprotein (HDL) toward apolipoprotein B-containing lipoproteins. However it may express some anti-atherogenic properties as well. Intracellular CETP increases cholesterol removal from peripheral cells and uptake by the liver (50). Drugs that inhibit CETP such as torcetrapib, anacetrapib and dalcetrapib increase HDL-c levels. The idea that increasing HDL-c level via inhibiting CETP may decrease cardiovascular disease risk has been challenged by the failure of torcetrapib. Serious concerns remain regarding raising HDL-c via CETP inhibition (51).

Original researches

In a phase II trial on a novel dual PPAR agonist, aleglitazar, improvement in hyperglycemia along with favorable effects on HDL-c and triglycerides has indicated with an acceptable profile. Aleglitazar is currently being studied in large clinical trials to explore its effects on cardiovascular endpoint in patients with diabetes and coronary disease (52).

In a randomized, open-label cross over study in patients with type 2 diabetes mellitus and athero-

genic dyslipidemia, effects of atorvastatin and combined therapy with fenofibrate on Proprotein convertase subtilisin kexin/type 9 (PCSK9) level has been explored. Results indicated that fenofibrate and atorvastatin increase circulating PCSK9 in diabetic patients with no additive effects (53).

In a double-blind randomized cross over study effect of fenofibrate on serum PCSK9 and VLDL particle concentrations in patients with type 2 diabetes who were receiving statin investigated. Fenofibrate decreased both serum PCSK9 and VLDL particle concentrations. The finding supports possible effect of PCSK9 on VLDL receptor degradation and VLDL metabolism (54).

Osteoporosis

Mechanisms involved in maintenance of bone mass and factors affecting them have not been fully elucidated yet. Studies which have been done in osteoporosis mainly focused on these factors and clarifying the effects of some widely used class of drugs on bone health.

Original researches

Preliminary reports indicate that oxidative stress and interleukins, particularly TGF- β 1 affect the maintenance of bone mass. Oxidative stress status and level of TGF- β 1 in blood and saliva of osteoporotic subjects have been compared with healthy subjects. Patients with osteoporosis had increased oxidative stress while there were no differences in TGF- β 1 levels between two groups. Supplementation of antioxidants may be helpful in osteoporotic patients (55).

The role of inflammatory mediators in osteoporosis had been demonstrated in recent years. The beneficial effects of n-3 fatty acids, potent anti-inflammatory substances, were explored in many animal studies. Effects of n-3 fatty acids on bone biomarkers were evaluated in postmenopausal women with osteoporosis. Results indicated that n-3 fatty acids can decrease bone resorption but they don't have significant effects on bone formation. Further studies are needed to clarify their role in treatment of osteoporosis (56).

Reviews

Maintenance of bone mass is influenced by genetic and environmental factors which modulate the local and systemic mechanisms which regulate bone turnover. One of the factors that seems to significantly influence bone mass is oxidative stress. Literature review in this area revealed that oxidative stress by itself and partly by influencing the regulatory cytokines such as tumor necrosis factor and interleukins involves in osteoporosis (57).

There were some growing evidences regarding the negative effects of homocysteine on bone mass. Literature review showed that homocysteine has considerable negative effects on bone markers, bone mineral density and fracture risk. Vitamin B deficiency per se may affect bone metabolism, which needs to be further investigated (58).

In order to clarify the role of n-3 fatty acids in bone health and osteoporosis, evidences in this area were reviewed. In general, animal studies support the beneficial effects of n-3 fatty acids in osteoporosis. However in human studies, there were various study designs and controversies over the outcomes. So it is difficult to come to a conclusion about the efficacy of n-3 fatty acids in prevention or treatment of osteoporosis (59).

Prostaglandins, especially E and F series are other factors that are important in bone physiology. Prostaglandins affect activity of osteoclasts, differentiation of osteoblasts and fracture healing process. Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used class of drugs which may affect bone health by reducing synthesis of prostaglandins thorough inhibiting cyclooxygenase (COX) enzymes. Review of evidences indicated that NSAIDs have shown anti-resorptive properties in animal studies and few human studies, but there were no conclusive results in bone formation. Higher bone mineral density was reported in some limited studies in daily administration of NSAIDs (60).

B-blockers are commonly used medications for variety of medical problems but their effect on bone is an issue of concern. Animal studies support their protective effects on bone but results of human studies are controversial. Reviewing the

literature indicated that studies in this area mostly have some limitations such as small sample size or lack of considering patients' body mass index (BMI), smoking behavior and lifestyle, which all can be a source of bias. Further well design trials is recommended to explore effects of this class of medications on bone health (61).

Emerging therapies

Emerging therapies and new targets for treatment of osteoporosis have been reviewed by Salari sharif and Abdollahi. The followings have discussed in this review:

Sclerostin antibody, LDL-receptor related protein 5, Cathepsin K inhibitors, Matrix metalloproteinases, selective androgen receptor modulators, cell adhesion molecules, L-carnitine, Amylin and adrenomedullin, Insulin-like growth factors, Reveromycin A and stem cells in fracture repair (62).

Conclusion

Though this chapter is not complete in all the aspects, this clears the status about the field of studies that carried out recently in the field of endocrine pharmacology. Interestingly, most of studies have been done in the recent 5-8 years that is in parallel to the growth of science of traditional medicine in the world. More interestingly, some of basic studies have gone on the direct line to complete preclinical safety and efficacy and also some clinical trial phases have been conducted properly. In this way, invention and introduction of Angipars (Semelil) for therapy of diabetic foot ulcer is a good example. On the other hand, there are many non-clinical studies that have proved efficacy of many naturally-derived compounds in endocrine diseases like diabetes but these studies were not continued at clinical stages to reach a drug. In other words, very few researchers have continued their work on the line to bring out appreciable products with clinical significance. Having great history of medicine and scientists and a great potential of natural sources, world deserve much better on-line activities to reach effective drugs. However, it is appreciable that, some researchers

have given novel ideas that deserve investment by grant bodies to reach out quality works. We believe that science of endocrine pharmacology is still young and more quality studies are still needed to introduce effective cure for disease like diabetes and osteoporosis or even obesity and lipid disorders.

Ethical considerations

Ethical issues (Including plagiarism, Informed Consent, misconduct, data fabrication and/or falsification, double publication and/or submission, redundancy, etc.) have been completely observed by the authors.

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