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THERAPEUTIC EFFECT OF METFORMIN AND NEBOVOLOL IN HIGH FAT DIET

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ABSTRACT

Obesity stands as a major health challenge in the Western world, presenting increased risks of diabetes (type 2), cardiovascular morbidity, cancer, and imposing significant economic costs on healthcare providers. The condition results from an imbalance between food intake and energy expenditure, often exacerbated by environmental factors such as readily available high-calorie food and sedentary lifestyles. Genetic factors also contribute to this imbalance. This study explores the potential of therapeutic agents to address obesity-related concerns, focusing on the regulation of appetite through complex hypothalamic neurocircuitry. Uncoupling proteins (UCP), specifically UCP1, play a role in energy metabolism and thermogenesis. Nebivolol, a third-generation β1 adrenoceptor blocker used for hypertension, has recently shown lipolytic action on human visceral adipocytes and activates UCP1, contributing to thermogenesis and weight loss. Metformin, an antidiabetic drug, is also examined for its effects on obesity. Metformin activates AMP-activated protein kinase (AMPK), inhibits mitochondrial respiratory chain function, and promotes glucose uptake. It has demonstrated lipid-lowering potential and is explored for its impact on cancer cells. The methodology involves an extensive literature survey using various online and offline resources, including research articles, reviews, and databases such as NEJM, Science Direct, PubMed, Sci-Hub, and Library Genesis. Current approaches to treating obesity encompass comprehensive lifestyle management, including diet, physical activity, and behavior modification. Multidisciplinary programs have shown modest long-term weight loss. Metformin and nebivolol present promising avenues for obesity treatment, leveraging their diverse pharmacological actions. Further research is essential to elucidate their mechanisms and optimize their clinical applications in the context of obesity management.

Keywords: Obesity, Metformin, Nebivolol, etc.

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INTRODUCTION

Obesity is the major health burden in the western world, in terms of increased risk of diabetes (type2), cardiovascular morbidity, cancer and also in economic costs to healthcare providers. It is characterized with accumulation of excess fat in body causing adverse effects on health. Obesity occurs when the balance between food intake and energy expenditure is disrupted, i.e., more food is consumed than utilized, leading to excess fat stores being laid down. There are many environmental factors that predispose individuals to gain weight, e.g., freely available high-calorie food and sedentary life style. Genetic factors also contribute to this imbalance. In the severely obese, surgical intervention may be necessary. An alternative approach is to develop therapeutic agents that can either reduce food consumption or increase energy utilization. The regulation of appetite relies on complex hypothalamic neurocircuitry in which the arcuate nucleus and the hormone leptin, ghrelin play important roles. Uncoupling proteins (UCP) uncouples respiration from oxidative phosphorylation and may contribute to obesity through effects on energy metabolism. The uncoupling activity of UCP1 is explained by its ability to transport protons in particular when fatty acids bind to the protein. Because basal metabolic rate is decreased in obesity, UCP expression is predicted to be reduced in obesity [1]. Nebivolol is a highly selective and long acting third generation β_1 adrenoceptors (AR) blocker. Nebivolol a third generation beta blocker, is used for the treatment of hypertension and it lowers blood pressure by reducing peripheral vascular resistance, Shows lipolytic action on human visceral adipocytes in recent ex-vivo studies. It has been observed that Nebivolol also has β_3 agonist effect and activates UCP1 (uncoupling proteins) which further induces gene expression in human visceral adipocytes, a pathway responsible for thermogenesis and weight loss [2]. Many studies based on the use of drugs activating β_3 adrenoceptors and other adrenoceptors confirmed that the sympathetic nervous system was the main trigger of UCP1 activation and induction (Bartness et al., 2010). Nebivolol upregulate expression of Uncoupling protein-1, increases thermogenesis and is a fat burning compound. The lower dysmetabolic effects of nebivolol may depend on its ß3 agonist activity on human visceral adipose tissue. Metformin an antidiabetic drug also has lipid lowering potential. Several reports revealed that metformin modulate the AMPK and thus it may have antiobesity potential.

METHODOLOGY

A thorough survey of literature was conducted on obesity and effects of metformin using various online and offline resources. The primary source of data collection was various research and review articles published by various publishers like Elsevier, PSCI, Springer, JDDT etc. Various online databases were also referred for collecting data on metformin and nebivolol.

The databases are NEJM, Science Direct, PubMed, Sci-Hub and Library Genesis. Some various other sources were gone through for the collection of literature on these drugs like various journals, book chapters and web pages to gather the maximum possible information.

Treatment of Obesity

The chief goal of obesity treatment is to maintain healthy weight. Treatment of obesity starts with comprehensive lifestyle management (i.e., diet, physical activity, behavior modification), which should include the following [3]. As with all chronic medical conditions, effective management of obesity must be based on a partnership between a highly motivated patient and a committed team of health professionals. This team may include the physician, a psychologist or psychiatrist, physical and exercise therapists, dietitians, and other subspecialists, depending on the co-morbidities of the individual patient. Multidisciplinary programs reliably produce and sustain modest weight loss between 5% and 10% for the long-term [4]. The preferred treatment modality for weight loss is dieting and physical exercise. But due to busy schedules and sedentary life-style follow-up the first two methods never seems to be practiced in a regular manner. On the other hand weight loss surgery runs out of the option considering the cost involved. There is a gradual shift towards an increase use of pharmacological medication [5]. Few medications are available for the treatment of obesity. At present, the only FDA-approved drugs for the long-term treatment of obesity are orlistat (Xenical), lorcaserin (Belviq), and the combination of phentermine and extended-release topiramate (Qsymia). There are medicinal strategies for weight loss: By reducing food intake either by augmenting the inhibitory effects of anorexigenic signals or factors that suppress food intake or by blocking orexigenic signals factors that stimulate food intake which lead to reduce the weight. Modulating the central controller regulating body weight by altering the internal reference value sought by the controller or increasing thermogenesis by uncoupling fuel metabolism from the generation of ATP, thereby dissipating food energy as heat. Fat blocking nutrient absorption in the alimentary canal, in particular, fat. Enhanced fat or protein turnover might reduce body weight by affecting either food or energy expenditure. Modulating the primary afferent signals regarding fat stores analyzed by the controller is also a one of the strategy to weight loss. This approach would have the potential advantage of forcing the endogenous controller to regulate multiple pathways of energy balance and minimize restitution. Drugs which are commonly used to control obesity are: Serotonergic agents like fluoxetine, dexfenfluramine, Fenfluramine. Nonadrenergic agents like amphetamine, phendimetrazine, phentermine, diethylpropion, pseudoephedrine, phenylpropanolamine, mazindol, noradrenergic and serotonergic agents like sibutramine. Orlistat (pancreatic lipase inhibitors) is standard drug as anti-obesity agent.

Centrally acting drugs (anorectic or appetite suppressants) are sibutramine, rimonabant. Some drugs have suppressive effect on food intake (promotes feeling of satiety) like Liraglutide, a glucagon-like peptide-1 analogue (incretinmimetc), exenatide (analogue of the hormone GLP-1), Pramlintide (synthetic analogue of the hormone Amylin) are also used in the treatment of obesity. The treatment which is preferred for the weight loss is physical exercise and dieting. But in todays world, due to the sedentary lifestyle and the busy schedules, these methods are not practiced on everyday basis and hence results are not seen. Weight loss surgery (bariatric surgery) is also an option to treat obesity but due to the cost involved in this treatment, it is not effectively used. Due to these reasons, the focus to treat the obesity is shifted towards the drug usage. Orlistat is the only medication which is approved by FDA as an anti obesity drug. It reduces the intestinal fat absorption by inhibiting the pancreatic lipase. Rimonabant is the second drug which had been approved in Europe for the treatment of obesity but it has not received any kind of approval in United States and Canada due to the safety issues [6].

AMPK dependent oxerigenic effect

Once activated, AMPK leads to a switch from anabolic to catabolic pathways; with the aim of restoring energy balance, ATP production is increased and ATP utilising pathways are inhibited. Hypothalamic AMPK plays a vital role in the regulation of food intake [7,8]. Constitutively active AMPK increases both food intake and body weight; whereas dominant negative AMPK expression in the hypothalamus is sufficient to reduce food intake and body weight [9]. The peripheral hormones ghrelin [10,11] and adiponectin both have hypothalamic AMPK implicated in their orexigenic effects. Hypothalamic AMPK has also been suggested as the mediator of the orexigenic effects of several other metabolic hormones and neuropeptides/modulators including cannabinoids [12] and glucocorticoids [13].

Metformin

Metformin is the first line medication for the treatment of type 2 diabetes, particularly in people who are overweight. Metformin was discovered in 1922. It is one of the most effective and safe medicine needed in a health system according to the World Health Organization's List of Essential Medicines. Metformin causes the activation of AMP-activated protein kinase (AMPK), inhibition of mitochondrial respiratory chain, activation of protein kinase A, inhibition of glucagon induced elevation of cyclic adenosine monophosphate (cAMP). Metformin ameliorates hyperglycemia without stimulating insulin secretion, promoting weight gain, or causing hypoglycaemia. Two effects, decreased hepaticglucose production [14,15] and increased skeletal myocyte glucose uptake have been implicated amajor contributors to glucose-lowering efficacy. Metformin also decreases hepatic lipids in obese mice however, a low-potency compound that is used at high doses, result in only modest net efficacy; in addition, significant side effects can occur. Metformin has an oral bioavailability of about 50-60%, under fasting conditions. The plasma protein binding of metformin is negligible and has an apparent high volume of distribution (300-1000 l after a single dose). Metformin is not metabolized. it is cleared from the body by tubular secretion, and exchanged in the urine. It is undetectable in blood plasma within 24 hours of a single dose. Some side effects which are caused by taking metformin are diarrhea, discomfort, nausea, flatulence, drowsiness, abdominal pain, tachycardia, vomiting, and rarely hypoglycemia or hyperglycemia.

Metformin and cancer

Accumulating evidence indicates that metformin inhibits growth, survival, and metastasis of different types of tumor cells, including those from breast, liver, bone, pancreas, endometrial, colorectal, kidney, and lung cancers [16]. Metformin's anticancer properties depend on its direct and indirect regulation of cells' metabolism. The direct effects are mediated by AMPKdependent and -independent pathways. (i) Metformin activates AMPK, which leads to the inhibition of mTOR signaling, and as a result, protein synthesis is disturbed, and cell growth and proliferation is suppressed. For example, crosstalk between G protein-coupled receptors (GPCRs) [17] and insulin receptor signaling systems may be inhibited by metformin: possibly contributing to the inhibition of pancreatic cancer proliferation. P53 is considered as a critical tumor suppressor gene in human cancers. Research showed that p53 is involved in the anti-cancer effects of metformin. Metformin activates AMPK and then induces p53 phosphorylation to prevent cell invasion and metastasis. (ii) Metformin also inhibit mTORC1, a key regulator of cell growth that can integrate intracellular and extracellular stimuli (58), in an AMPKindependent manner. Additionally, metformin suppresses mitochondrial complex I, thereby preventing the generation of reactive oxygen species (ROS) and further decreasing DNA damage, suppressing cancer development [18]. Previous studies also suggested that metformin can suppress cancer development by activating autophagy and apoptosis through an AMPK independent pathway.

Pharmacology of Nebivolol

Adipose tissue has two components, namely white adipose tissue (WAT) and brown adipose tissue (BAT). WAT provides most of the total body fat and is the origin of fatty acids that are used as energy substrates. It is now known that excessive adiposity results in excessive circulation of fatty acids along with inflammatory adipokines, TNFa and IL-6 contribute to the insulin resistance, diabetes mellitus 2, hyperlipidemia, and hypertension, which contribute to the metabolic syndrome. BAT exists within posterior neck fat pads in neonates to provide cold adaptive thermogenesis for new borns that have inadequate hair to protect against heat loss. The fundamental function of BAT is thermogenesis. Neonatal BAT depots are lost soon after newborn period since muscles and skin hair undertakes the function of heat production and preservation. However recent studies, especially nuclear medicine studies, which incidentally showed increased flourodeoxy glucose uptake by some non-neoplastic tissues, revived the interest in BAT [19]. It has been shown that BAT can be up regulated as an adaptation to cold climate. BAT is metabolically more active, has a richer vascular supply and innervation compared with WAT. Heat production is achieved by uncoupling protein 1 (UCP1). Recent studies also have shown that BAT was present mixed with WAT, in a ratio of 1 brown to 200 white fat cells. Since high metabolic activity and dissipating energy as heat instead of fat storage, BAT theoretically can be used as a way of consuming excess energy results from overeating and insufficient physical exercise. Some murine models have confirmed this hypothesis, in one of which mouse strains with ectopic BAT deposits in skeletal muscle responded to over feeding by increased BAT oxidation and therefore protected against obesity. Induction of BAT in feocromocitoma patients and by cold weather lends support to differentiation of WAT into BAT. Both BAT and WAT have extensive sympathetic nervous system innervations and beta-3 adrenergic receptors. Adrenergic stimuli through the activation of beta-3 adrenoceptors transform the white adipocytes into brown ones. Furthermore mice lacking beta-3-adrenoceptors have a significant reduction of this transformation. Beta-3 adrenergic agonists in animal models demonstrated increased energy expenditure and fat oxidation, selective loss of fat and preservation of lean body mass, improvement in insulin sensitivity beyond expectations from weight loss [20]. However, none of the available drugs, which are pure beta-3 adrenoceptor agonists, could successfully passed phase-II studies. Nebivolol is a third generation beta blocker which has high beta-1 selectivity. Its main mechanism of action is enhancing nitric oxide, a vasodilator, anti-platelet and anti-oxidant molecule, through endothelial cells. Nebivolol also is a partial agonist of beta-3 receptors. Some clinical evidence also suggested the beneficial effects of nebivolol on lipid profile and insulin resistance through beta-3 receptor agonism. We think that because no pure beta-3 receptor agonists approved for clinical use are present at the time, although a partial agonist of beta-3 receptors, nebivolol can be used to induce brown (or in other words ‘‘good fat”) fat. Along with anti-platelet, antioxidant and vasodilatory effects, anti-obesity effect of nebivolol may be an effective and safe option in metabolic syndrome which is main consequence of obesity.

Nebivolol combines the properties of a β1-adrenoceptor (AR) antagonist (β1-blocker) and a β3-AR agonist. In human myocardium, β3-ARs are expressed both on endothelial cells of the coronary microvasculature and on cardiac myocytes. (Left) Activation of β3-ARs on coronary endothelium produces the activation of endothelial nitric oxide synthase (NOS) and the release of nitric oxide (NO) and of an endothelium-derived hyperpolarizing factor (EDHF), both of which contribute to increased vasodilation and coronary perfusion. In addition, NO may paracrinally promote cardiomyocyte relaxation and left ventricular (LV) diastolic filling, thereby enhancing diastolic reserve. (Right) In ventricular cardiomyocytes, nebivolol combines the effects of β1-AR blockade, which prevents the deleterious effects of chronic adrenergic stimulation on myocardial remodeling, and activation of β3-AR; the latter, through G-alpha-i coupling, (e)NOS activation and NO production may oppose the acute effects of adrenergic stimulation of contractility. Hypothetically, agonism on β3-ARs may contribute to additional protection against adverse remodeling under chronic adrenergic stress through sustained functional antagonism of the β1-AR/cyclic adenosine monophosphate (cAMP) pathway or other (yet undetermined) pathways. The combined effects on remodeling, ventricular perfusion and filling ultimately would result in improved LV function [21-24].

CONCLUSION

Metformin is a widely used clinical drug with numerous benefits, which through different signaling pathways. The most remarkable feature of metformin is anti-hyperglycemia. Nebivolol a antihypertensive drug also have beneficial effects in metabolic syndrome. In conclusion we can say that these drugs can be useful in obesity.

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