WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

An Overview of Chronopharamcology and it's Role on Diabetes Malitus

Tejmal Premsing Rathod [1], Snehal Ashok Patil [2], Swapnil Bandu Jadhav[3], Rutuja Ramesh Yeole[4]

[1,2,3,4]Dr. Uttamrao Mahajan college of B pharmcy,Chalisgaon Dist.Jalgaon,424101

ABSTRACT

The concept that an organism's response to a medicine may depend on the hour of delivery is supported by chronobiological findings. The idea that a drug's desired and undesirable effects may change depending on when it is administered was first put forth by Virey in 1814 (Reinberg 1979). This theory was later confirmed, as it was discovered that the timing of medicine delivery affects both the toxicity and effectiveness of numerous medications. The science of chronopharmacology examines how biological time and endogenous periodicities affect how medications work. The major goal is to foresee changes in both desired effects and pharmaceutical tolerance. When used within the permitted parameters, chronotherapy should not be toxic.

The pharmacodynamics (i.e., potency and toxicity) and pharmacokinetics (i.e., how they behave within the body) of drugs can be significantly influenced by the time of day when taken. Few drugs, especially those used to treat cancer, have had their chronopharmacokinetics investigated. We have shown that pretreatment with melatonin or steroids can alter the toxicity and chronopharmacokinetics of drugs.

Keywords:- Diabetes mellitus: Types of Diabetes mellitus, Chronopharmacology: Chronopharmaceutics, Chronopharmacokinetics, and Chronotherapeutics

Introduction:

Nearly all functions of the body, including those influencing pharmacokinetic parameters such as drug absorption and distribution, drug metabolism and renal elimination, show significant daily variations:

these include liver metabolism, hepatic blood flow and the first-pass effect; glomerular filtration, renal plasma flow and urine volume and pH; blood pressure, heart rate and organ perfusion rates; acid secretion in the gastro-intestinal tract and gastric emptying time.

The onset and symptoms of diseases such as asthma attacks, coronary infarction, angina pectoris, stroke and ventricular tachycardia are circadian phase dependent. In humans, variations during the 24 h day in pharmacokinetics (chrono-pharmacokinetics) have been shown for cardiovascularly active drugs (propranolol, nifedipine, verapamil, enalapril, isosorbide 5-mononitrate and digoxin), anti- asthmatics (theophylline and terbutaline), anticancer drugs, psychotropics, analgesics, local anaesthetics and antibiotics, to mention but a few. Even more drugs have been shown to display significant variations in their effects throughout the day (chronopharmacodynamics and chronotoxicology) even after chronic application or constant infusion.

Moreover, there is clear evidence that even dose/concentration-response relationships can be significantly modified by the time of day. Therefore, circadian timing should be considered as an important factor influencing the pharmacokinetics of a drug and its effects or side effects.

There is compelling scientific work indicating that extra caution is needed when using the drug. Most prescribers today are more concerned with the “what” of prescribing rather than the “when” of prescribing.

Chronopharmacology, the study of physiological response to drugs as a function of time and its relationship to current drug therapy is discussed. The goal of chronotherapy is to apply the principles of chronology to the treatment of human diseases. Suitable patients for treatment over time are those taking high-risk medications, those with high-risk diseases (eg, cancer), or those receiving high-risk treatment. take a cigarette. Although little is known about the circadian timing characteristics of many drugs or diseases, researchers should consider possible relationships between circadian timing and drug action when designing clinical trials. treatment trial. Drug therapy can be optimized by tailoring the dosage regimen and delivery system to the biological temporal pattern.

Chronobiology is the science that studies the rhythms of each biological process or function of living organisms. On the other hand, chronological pharmacology is the science that studies the optimization of drug dosages in order to maximize effectiveness and minimize side effects by administering drugs according to circadian rhythms. Simply put, if we take drugs according to our biological clock, they can be more beneficial and cause the fewest side effects. There are three subdivisions of chronological pharmacology, where chronological therapy pinpoints when patients are most at risk and most in need of treatment. This principle is used to treat diseases such as cardiovascular disease and many others.

* CHRONOPHARMACOLOGY

Chronopharmacology, the study of time-dependent physiological response to drugs, and its relationship to current drug therapy are discussed. The objective of chronotherapy is to apply chronobiologic principles to the treatment of human disease.The appropriate patients for chronotherapy are those who are receiving high-risk drugs, who have a high-risk disease (e.g., cancer) or who are receiving a high-cost drug. Although little is known of the chronobiologic characteristics of many drugs or diseases, researchers should take into account the possible relationship of chronobiology to drug effects when designing therapeutic trials. Drug therapy can be optimized by tailoring dosing schedules and distribution systems to chronobiologic patterns.

Chromopharmacology classified in following three types :

1. **Chronopharmaceutics**
2. **Chronopharmacokinetics**
3. **Chronotherapeutics**

1. **Chronopharmaceutics**:-

is the therapeutics field that designs and evaluates drug delivery devices capable of delivering drugs at a rate based on treatment needs.

2. Chronopharmacokinetics:-

This is the field that deals with rhythmic changes based on drug bioavailability and excretion. It has a drug-modifying effect in terms of absorption, distribution, metabolism and excretion. Several researchers have worked in this area to better optimize drugs. One such study reported that cardiovascular drugs, nonsteroidal anti-inflammatory drugs, anesthetics, antineoplastic agents, anti-asthmatics, and psychotropic drugs have better bioavailability when taken in the morning compared with with the evening.

3. Chronotherapeutics

It is a therapeutic approach performed in vivo, where drug availability is programmed to promote wound healing and minimize side effects. One technique to promote drug therapy is to use drugs when they are best tolerated. Prescribing medication at spaced intervals throughout the day helps to maintain an adaptive equilibrium with day-to-day variations. This approach is very effective in patients with heart, kidney, and liver failure because drug accumulation can be toxic and affect organs.

Ideal Characteristics of Chronopharmacotherapy:-

- The application of therapy over time helps make drugs non-toxic by removing the factors that cause them to work this way. It has actual times and specific biomarkers for each disease state.
- It works on a command framework.
- It is biodegradable and biocompatible.
- It can be produced at an economical cost. It can easily monitor patients and improve consistency in their dosing habits.

Why Is Chronopharmacology Necessary:-

Autoinduction

When a dose is repeated, enzyme levels increase to remove the drug. This process is called mobile vehicle induction. It can lead to a cure for a particular disease, but it depends on the dose and the attention given to the drug. The drug is released through self-induction whenever the body requires further administration. For example, carbamazepine works on the principle of time distribution.

Autoinhibition

This is the process of inhibiting drug metabolism. It is also known as allosteric inhibition or feedback inhibition.

Food Effects

The variation during the day comes from food intake. The gastric emptying of the drug depends on the food taken with the drug. If a person eats more food at night than breakfast and takes the drug, the absorption and transport to the liver for metabolism will be reduced. Therefore, the consumption of heavy foods by tablets may lead to a decrease in the bioavailability of the drug.

Advantages of Chronopharmacotherapy:-

This avoids drug overdose.

It allows you to make the best use of any medication that is used.

At the same time, it reduces excessive drug use and facilitates drug release over time.

Disadvantage of Chronopharmacotherapy:-

It is rarely used in patients due to its low success rate.

The patient should be awake until the next relaxation schedule. Patients advise professionals to save responses automatically. Need advanced technology.

This process requires a lot of construction and economics.

Mechanism of Chronopharmacology:-

Alterations in circadian and other rhythms in the biological susceptibility and response of organisms to a variety of physical and chemical agents, including drugs and food, are fairly common phenomena. Temporary differences in drug effects depend on endogenous circadian rhythms, including metabolism. In addition, temporal pharmacology studying the effects of drugs on parameters (e.g., circadian cycle, peak time, amplitude, and adjusted mean) was used to describe circadian rhythm. The periodic and thus predictable changes in drug effects can be better understood by looking at additional concepts:

1. Drug pharmacokinetic time, i.e. time-dependent change (rhythm) of parameters used to characterize drug pharmacokinetics (bioavailability), e.g. Cmax, tmax , AUC and t1/2;
2. Chronesthesia, i.e., rhythmic changes in the sensitivity of the target biological system to this drug, including CR in pharmacodynamic processes; And
3. Currentity, that is, the overall effect is integrated into the drug.

Chronopharmacology involves both the study of the effects of drugs based on circadian timing and the study of the effects of drugs on rhythmic characteristics.

Daily changes in the effects of various chemical agents have been observed:

histamine, sodium salicylate, acetylcholine, halothane, prostaglandin F, reserpine, cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orciprenaline and SCH 1000 (bronchodilator), indomethacin, ACTH, cortisol and various synthetic corticosteroids.

Chronopharmacology is useful in solving drug optimization problems, i.e. to increase the desired effect or reduce its side effects. In the human body (among other animals), the metabolic fate of a pharmacological agent (as well as that of a nutrient) is not constant over time. Thus, the biochronic approach to pharmacological phenomena has a lower risk of error and/or misinformation than the conventional homeostatic approach. One of the goals of pharmacological timing refers to the use of pharmacological timing in clinical treatment to improve both efficacy and tolerability of drugs by timing biological best for drug use.

Factors Affecting Chronopharmacology:

To optimize chronotherapeutic schedules (designs), we examined the interindividual differences in chronopharmacologic effects of drugs with consideration of the following three factors:

(a) Inherited factors of direct relevance to chronopharmacology (genetic variability, gender-related differences) as well as age- related differences;

(b) Interindividual difference in chronoeffectiveness related to disease (e.g., various types and stages of cancer, affective disorders, etc.) as well as to drug-dependent alteration (phase shifts, distortion) of biological rhythms; and

(c) Means to solve problems resulting from the need of individualization in chronotherapy. These involve the use of circadian marker rhythms (MR) whose characteristics (peak or trough time, amplitude, etc.) can be precisely quantified and thus are applicable as a reference system for physiologic, pathologic, pharmacologic and therapeutic uses.

The MR has to be specific and pertinent and must be easily monitored and documented. This approach can be further advanced by the use of a battery of MRs rather than a single MR. Other suggested means relate to the fact that chronobiotics (agents capable of influencing parameters of a set of biological rhythms) should be considered (e.g., corticoids and adrenocorticotropic hormone) and/or to the subject's synchronization should be enforced by "conventional" zeitgebers (e.g., bright light, physical activity).

* DIABETES MALITUS *

Diabetes is a disease that occurs when the amount of sugar (glucose) in your blood is too high. It develops when your pancreas doesn't produce enough insulin, if at all, or when your body doesn't respond properly to the effects of insulin. Diabetes affects people of all ages. Most forms of diabetes are chronic (lifelong) and all are manageable with medication and/or lifestyle changes.

Glucose (sugar) mainly comes from carbohydrates in your food and drinks. It is your body's main source of energy. Your blood carries glucose to every cell in your body to use as energy.

When glucose enters your bloodstream, it needs help — a "key" — to get to its final destination. The key is insulin (a hormone). If your pancreas doesn't produce enough insulin or if your body doesn't use it properly, glucose builds up in your blood, causing high blood sugar (hyperglycemia). Over time, persistently high blood sugar can lead to health problems, such as heart disease, nerve damage, and eye problems.

The technical name for diabetes is diabetes mellitus. Another disease with the same term "diabetes" - diabetes insipidus - but different. They have the common name "diabetes" because they both cause more thirst and frequent urination. Diabetes insipidus is much rarer than diabetes insipidus.

Types of Diabetic mellitus

Type 1 diabetes

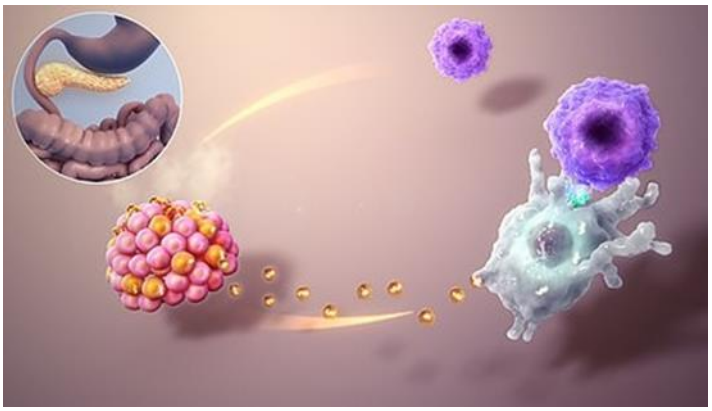
Type 2 diabetes Gestational diabetes

Type 1 diabetes

Type 1 diabetes is characterized by the loss of insulin-producing beta cells from the islets of the pancreas, resulting in insulin deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is immunological in nature, in which a T-cell-mediated autoimmune attack results in loss of beta cells and thus loss of insulin.[44] It is responsible for about 10% of diabetes cases in North America and Europe. Most of those affected were healthy and of a healthy weight at the time of illness. Insulin sensitivity and responsiveness are usually normal, especially in the early stages. Although it is called "juvenile diabetes" because of its frequency of onset in children, the majority of people with type 1 diabetes today are adults.

Fragile diabetes, also known as unstable diabetes or unstable diabetes, is a term traditionally used to describe significant and recurrent changes in glucose levels, often occurs for no apparent reason in insulin-dependent diabetes. However, the term is not important. biological basis and should not be used. However, type 1 diabetes can be accompanied by high, irregular, and unpredictable blood sugar levels and potentially cause diabetic ketoacidosis or low blood sugar. Other complications include impaired regulatory response to low blood sugar, infections, gastroparesis (resulting in uneven absorption of dietary carbohydrates), and endocrine diseases (eg. such as heart disease). Addison). These phenomena are thought to occur more infrequently in 1-2% of people with type 1 diabetes.

Type 1 diabetes is partially hereditary, with certain genes, including certain HLA genotypes, known to affect diabetes risk. In genetically predisposed individuals, the onset of diabetes may be triggered by one or more environmental factors [48], such as viral infection or diet. Several viruses have been found to be involved, but to date there is no solid evidence to support this hypothesis in humans.



Autoimmune attack in type 1 diabetes

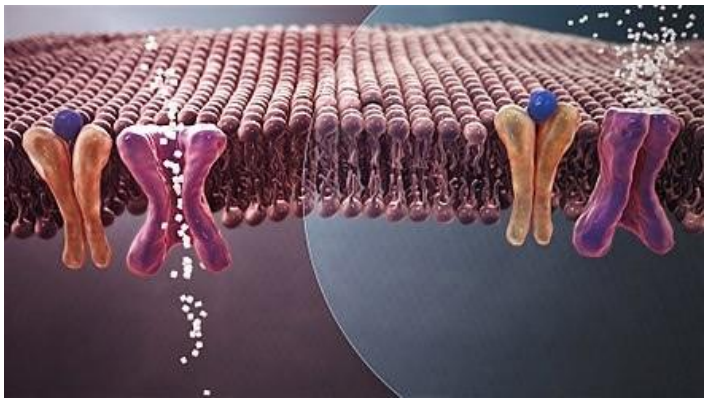
Type 1 diabetes can occur at any age, and a significant proportion is diagnosed in adulthood. Latent autoimmune diabetes of adulthood (LADA) is the diagnostic term used when type 1 diabetes develops in adults; Its onset is slower than that of similar conditions in children. Because of this difference, some people use the informal term "type 1.5 diabetes" to refer to the disease. Adults with LADA are often initially misdiagnosed as having type 2 diabetes, based on age, not cause.

Type 2 diabetes

Type 2 diabetes is characterized by insulin resistance, which may be associated with relatively decreased insulin secretion. THE The poor responsiveness of body tissues to insulin is thought to be related to the insulin receptor. However, the specific errors are not known. Cases of diabetes due to known defects were classified separately. Type 2 diabetes is the most common type of diabetes Diabetes accounts for 95% of all diabetes cases. Many people with type 2 diabetes have signs of prediabetes (decreased fasting blood glucose and/or glucose intolerance) before the criteria for type 2 diabetes were met. Progression of prediabetes Type 2 diabetes can obviously be slowed or reversed with lifestyle changes or medications that improve or decrease insulin sensitivity.

The liver produces glucose. Type 2 diabetes is mainly caused by lifestyle and genetic factors. Several lifestyle factors are known to be important for develop type 2 diabetes, including obesity (defined as a body mass index greater than 30), lack of physical activity,

poor diet, stress and urbanization. Excess body fat is associated with 30% of cases in people of Chinese and Japanese ancestry, 60-80% of cases are in people of European and African descent, and 100% in Pima Indians and Pacific Islanders.[13] Even people Non-obese may have a high waist/hip ratio.



Reduced insulin secretion or weaker effect of insulin on its receptor leads to high glucose content in the blood

Dietary factors such as sugary drinks are associated with an increased risk. The type of fat in the diet is also important, saturated and trans fats increase the risk of disease, and polyunsaturated and monounsaturated fats reduce the risk. Excessive consumption of white rice may increase the risk of diabetes, especially among Chinese and Japanese.[56] Lack of physical activity can increase the risk of diabetes in some people.

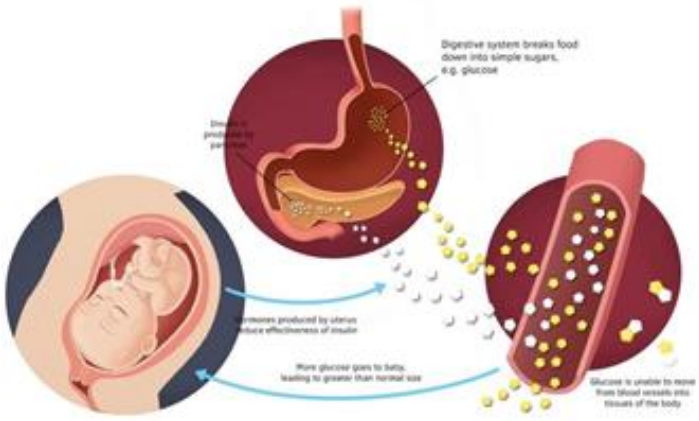
Negative childhood experiences, including abuse, neglect and family difficulties, increase the risk of type 2 diabetes in life by 32%, with neglect having a major impact best.

Side effects of antipsychotics (especially metabolic abnormalities, dyslipidemia, and weight gain) and unhealthy lifestyles (including poor diet and reduced physical activity) are potential risk factors.

Gestational diabetes

Gestational diabetes resembles type 2 diabetes in some respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2 to 10% of pregnancies and may go into remission or go away after delivery. It is recommended that all pregnant women get tested between 24 and 28 weeks of pregnancy. It is usually diagnosed during the second or third trimester because insulin antagonist hormone levels increase at this time. However, after pregnancy, about 5-10% of women with gestational diabetes develop another form of diabetes, most commonly type 2. Gestational diabetes is completely treatable but requires Special attention. medical supervision throughout pregnancy. Management may include dietary changes, blood sugar monitoring, and in some cases insulin may be required.

While it may be temporary, untreated gestational diabetes can harm the health of the unborn baby or the mother. The risks to the baby include a large baby (high birth weight), birth defects of the heart and central nervous system, and musculoskeletal defects. Elevated fetal blood insulin levels can inhibit fetal surfactant production and cause neonatal respiratory distress syndrome. High levels of bilirubin in the blood can be the result of destruction of red blood cells. In severe cases, perinatal death can occur, most commonly due to poor placental perfusion due to vascular damage. Induction of labor may be indicated if placental function is impaired. A caesarean section may be performed in cases where the fetus is significantly weakened or there is an increased risk of injury related to a large fetus, such as a difficult delivery of the shoulder.



Gestational Diabetes

Causes of Diabetes malitus:-

Causes of Type 1 Diabetes

Type 1 diabetes is thought to be caused by an autoimmune reaction (the body attacks itself by mistake). This reaction destroys cells in the pancreas that make insulin, called beta cells. This process can take months or years before symptoms appear.

Some people have certain genes (traits passed down from parents to children) that make them more likely to develop type 1 diabetes. However, many people will not develop type 1 diabetes, even if they do. gene. An environmental agent, such as a virus, may also play a role in the development of type 1 diabetes. Dietary habits and lifestyle do not cause type 1 diabetes.

Causes of Type 2 Diabetes

The most common form of diabetes is caused by a number of factors, including lifestyle factors and genes.

Overweight, obese and inactive

You are more likely to develop type 2 diabetes if you are not physically active and if you are overweight or obese. Being overweight sometimes leads to insulin resistance and is common in people with type 2 diabetes. The location of body fat also makes a difference. Excess belly fat has been linked to insulin resistance, type 2 diabetes, and cardiovascular disease. To find out if your weight puts you at risk for type 2 diabetes, check out this body mass index (BMI) chart.

Insulin resistance

Type 2 diabetes usually begins with insulin resistance, a condition in which muscle, liver, and fat cells don't use insulin well. As a result, your body needs more insulin to help glucose get into your cells. At first, the pancreas produces more insulin to meet the extra demand. Over time, the pancreas no longer produces enough insulin and blood sugar levels rise. Genes and family history Like type 1 diabetes, certain genes can make you more likely to develop type 2 diabetes. The condition tends to run in families and occurs more often in racial/ethnic groups. after:

African American Alaska Natives Native American Asian Americans

People of Hispanic/Latin descent Native Hawaiians

pacific islanders

Genes may also increase the risk of type 2 diabetes by increasing the tendency to be overweight or obese.

Course of Gestational diabetes

Scientists believe that gestational diabetes, a type of diabetes that develops during pregnancy, is caused by hormonal changes related to pregnancy as well as genetic and lifestyle factors.

Insulin resistance

The hormones produced by placental NIH external binding contribute to insulin resistance, which occurs in all women in late pregnancy. Most pregnant women can produce enough insulin to overcome insulin resistance, but some cannot. Gestational diabetes occurs when the pancreas does not produce enough insulin.

Like type 2 diabetes, being overweight has been linked to gestational diabetes. Women who are overweight or obese may have developed insulin resistance during pregnancy. Excessive weight gain during pregnancy can also be a cause.

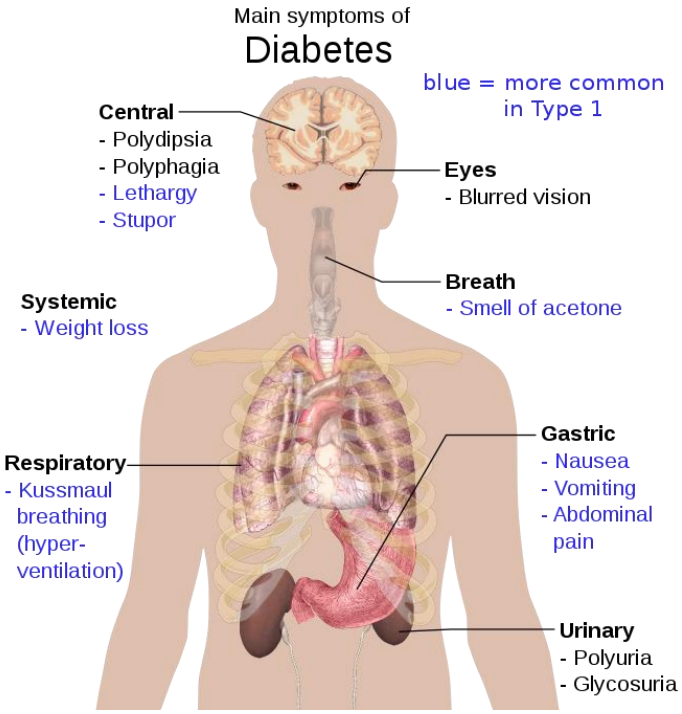
Hormonal changes, extra weight, and family history can contribute to gestational diabetes

Genes and family history

A family history of diabetes makes women more likely to develop gestational diabetes, which suggests that genes play a role. Genes may also explain why the disorder occurs more frequently in African-Americans, Indian-Americans, Asians, and Hispanics/Latinos.

Signs and Symptom Diabetes:-

The classic symptoms of untreated diabetes are unintentional weight loss, polyuria (increased hunger), polydipsia (increased thirst), and binge eating (increased hunger). Symptoms can develop quickly (weeks or months) in type 1 diabetes, while they often develop much more slowly and may be difficult to detect or absent in type 2 diabetes. Other signs and symptoms may mark the onset of diabetes, although they are not specific to each disease. sick. In addition to the known symptoms listed above, they include blurred vision, headache, fatigue, slow-healing cuts, and itchy skin. Prolonged high blood sugar can cause glucose to be absorbed into the lens of the eye, resulting in a change in shape, resulting in vision changes. Long-term vision loss can also be caused by diabetic retinopathy. Some of the skin rashes that can occur with diabetes are collectively known as diabetic dermatoses.



Overview of the most significant symptoms of diabetes

Treatment of Diabetes mellitus

Taking insulin or other diabetes medications is often part of diabetes treatment. Along with making healthy food and drink choices, being active, getting enough sleep, and managing stress, medication can help you manage this condition. Several other treatment options are also available.

* ROLE OF CHROMOPHARMACOLOGY ON DIABETES MALITUS *

Chronopharmacology is the study of how the effects of drugs evolve according to circadian and endogenous cycles. The primary goal is to predict changes in desired effects and tolerability.

Temporary therapy must be non-toxic within the approved limits of use. It must have a specific trigger biomarker for a given disease. It should have a feedback control system. Especially in the case of parenteral administration, biocompatibility and biodegradability are required. It must be easy to use for the patient to improve adherence to the dosing regimen.

It does not contain any drugs and is most effective when a person sleeps for several hours. But the downside of timed therapy was that she suffered from insomnia 24 hours after the treatment because the patient fell asleep during the treatment. This person becomes less effective in therapy over time and this takes time, so they have to pause their hectic routine. Patients should see their doctor regularly to avoid side effects. The person may sometimes feel hot or cold.

The challenges of modern life can be managed to better align with our circadian rhythms. To have less of an effect on blood sugar, you can eat a high-carb meal during the day instead of at night. Light therapy and melatonin supplements can be used to tailor circadian rhythms to their lifestyle and eating habits. Blood sugar and many diseases related to uncontrolled blood sugar are related to the body's internal clock. Modern humans would certainly benefit from knowing how to make simple lifestyle changes to improve their overall health.

Glucose homeostasis is one of the most fundamental physiological processes in mammals controlled by the temporal system, as it relies heavily on the system's predictive ability to coordinate metabolic function. metabolism. metabolism with daily variation in nutrient absorption. . Studies in humans and rodents have confirmed that daily rhythms of blood sugar and insulin secretion are regulated by a temporal system. Molecular clocks are essential for glucose metabolism, as evidenced by impaired glucose tolerance and insulin sensitivity when central clock gene expression is disrupted. Although SCN-mediated autonomic and neurogenesis affect glucose homeostasis, the peripheral clocks in the liver and pancreas also play a role in glucose management.

The most important rhythm regulated by the internal synchronization system in mammals is the sleep/wake cycle. For a while, it was noticed that people with metabolic diseases, including obesity, glucose intolerance or diabetes, also had difficulty sleeping. The most common is sleep apnea, which includes obstructive sleep apnea. Insufficient sleep and/or poor sleep quality are important risk factors for obesity and metabolic cardiovascular disease. A large proportion of patients with insomnia (more than 50%) have comorbidities, including cardiovascular disease, mental illness, obesity, and diabetes. In contrast, patients with type 2 diabetes often have higher rates of insomnia, with studies indicating that about 50% of adults with diabetes have insomnia, compared with about 30% of those without the disease. diabetes. Other sleep disturbances, such as decreased sleep duration or inadequate sleep, have been reported in people with type 2 diabetes. Recently, sleep duration was reported to be a strong predictor on cardiovascular metabolic risk in obese adolescents. A large study of nurses' health found that people who slept less than 5 hours a night had a higher risk of being diagnosed with symptomatic diabetes. If it is true that short or irregular sleep is an independent risk factor for obesity and poor glycemic control, it may be possible to improve sleep quality to improve these outcomes. The opposite is also possible

The circadian rhythm is controlled by a biological clock located in the hypothalamus, called the suprachiasmatic nucleus. Timing therapy, a branch of drug therapy, plays an important role in the treatment of various disorders, such as providing benefits at the right time, in the right place, and in the same amount. beneficial to the patient.

The timing aspects of pharmacology are important in the management of diurnal diabetes, as the duration of daily physical activity and the patient's drug therapy have an effect on the course of diabetes. . increase blood sugar. This leads to an increased risk of obesity, diabetes, increased cardiovascular morbidity and mortality. According to a savior physician working on issues related to diabetes, plasma glucose levels change independently of dietary habits as well as insulin and medication intake. People suffering from the dawn phenomenon are very difficult to solve, so the basic goal is to detect the operation of the biological clock in the human body and its healing effects over time on humans, contributing to increasing efficiency. treatment and reduce side effects. .

With these points in mind, this review attempts to discuss the role of palliative therapy in diabetes control, as well as the various techniques used in the formulation and design of drug delivery systems. time therapy and legal issues related to time therapy.

CONCLUSION

The most recent discoveries that we have highlighted provide new understanding of the burgeoning discipline of chronopharmacology as well as the molecular underpinnings of the changes in PK/PD that have been noted in a great number of situations. Many significant questions are still unsolved, though. These conclusions are supported by the majority, if not all, of the circadian expression data at the genome level that are exclusively accessible for rats. Extrapolating these findings to humans is not a given given that the expression and functional characteristics of drug-metabolizing enzymes and drug transporters are extremely species specific (162). Significant advancements in the characterisation of circadian changes in protein expression and activity in humans are urgently required to convert research findings to clinical application.

Frequent and therefore predictable changes in biosensitivity and response to a wide variety of physical and chemical agents can now be considered a fairly common phenomenon. Chronopharmacology includes both the study of drug effects based on circadian timing and the study of drug effects on rhythmic features (cycle, tau, acrophase, phi, amplitude, a, and mesor rhythms, M). Illustrative examples of circadian time (24 h uniform tau) pharmacology in humans are summarized in the updated tables, noting that objective substantiation of temporal pharmacological data requires Use the appropriate method. Daily changes in the effects of various chemical agents have been observed:

histamine, sodium salicylate, acetylcholine, halothane, prostaglandin F2alpha, reserpine, cyproheptadine, ethanol, insulin, chlorothiazide, oxymetholone, orcinprenaline and SCH 1000 (hereinafter a bronchodilator), indomethacin, lignocaine, ACTH, cortisol, and synthetic corticosteroids different. Although pharmacological information is well documented in humans regarding circadian rhythms, studies are not limited to a 24-hour period but have been extended to menstrual rhythms, e.g. approximately 30 days as well as about 1 year. To better understand pharmacological outcomes over time, three new concepts should be considered:

a) drug pharmacokinetic time, defined as both changes in the circadian rhythm (and/or pharmacokinetic effects) of the drug and excretion (urinary, among other factors); b) symbiosis of the biological system to the drug or circadian variation in the sensitivity of any biological system to the drug (including organ systems, tumors, parasites, etc.); and c) The chronology of a drug or the rhythmic change in the overall effect and effectiveness of a drug. This term takes into account the kinetic and sensory times of the biological systems involved. Currently, one of the goals of pharmacology over time is to solve the problems of drug optimization, that is, to improve the desired effect of corticosteroids or other drugs, while reducing undesirable effects. desire. Metabolic pathways are neither permanently open nor open with constant permeability on a 24-hour scale, among other biological domains. Thus, the biochronic approach regarding pharmacological phenomena has a lower risk of error and/or misinformation than the conventional homeostatic approach.

The recent findings we have highlighted provide insight into the evolving field of temporal pharmacology and the mechanistic basis of the PK/PD variants that have been observed in a large number of cases. However, many important questions remain unanswered. Most, if not all, of the gene-level bio expression data on which these conclusions are based are only available for rodents. Considering that the expression and functional characterization of drug-metabolizing enzymes and drug transporters are highly species-specific (162), extrapolating these results to humans is unavoidable. . To translate research data into clinical applications, significant progress in characterizing biological variations in human protein expression and activity is absolutely necessary. Although the impact of the circadian clock on health, disease, and treatment has received more attention in recent years, these findings have yet to be applied to clinics or institutions. large scale management. Entering a biological search term on the ClinicTrials.gov website will yield a list of 205 related clinical trials. Twelve of these trials focused on cancer, but none aimed to establish time therapy regimens. The keyword time therapy yielded 14 results. In contrast, the search term cancer produced 38,331 results. Similar results were obtained from the EU Register of Clinical Trials. Given that about 20% of the transcriptional, proteomic, and metabolic systems are under clock control (34, 163, 164), these results seem disproportionate. In the case of regulatory agencies, none of the biological temporal effects on PK/PD described here are covered by the guidelines issued by the International Conference on Harmonization of Technical Requirements in Registration pharmaceuticals for human use (ICH). This is surprising, especially since hepatotoxicity and undesirable cardiac side effects are the most common reasons people stop taking commercially available medications.

*** REFERENCE***

1. Moore RY, Eichler VB. Loss of a circadian adrenal corticoste-rone rhythm following suprachiasmatic lesions in the rat. BrainRes. 1972;42:201–206.
2. BassJ,TakahashiJS.Circadianintegrationofmetabolismandenergetics. Science.2010;330:1349–1354. Albrecht U. Timing to perfection: the biology of central andperipheralcircadian clocks. Neuron.2012;74:246–260. Panda S, Antoch MP, Miller BH, Su AI, Schook AB, Straume M,etal.Coordinatedtranscriptionofkeypathwaysinthemouseby the circadian clock. Cell. 2002;109:307–320.
3. UedaHR,ChenW,AdachiA,WakamatsuH,HayashiS,Takasugi T, et al. A transcription factor response element forgeneexpressionduringcircadiannight.Nature.2002;418:534–539. HughesME,DiTacchioL,HayesKR,VollmersC,PulivarthyS,BaggsJE,etal.Harmonicsofcircadiangenetranscriptioninmammals. PLoSGenet.2009;5:e1000442.
4. KoikeN,YooSH,HuangHC,KumarV,LeeC,KimTK,etal. Transcriptionalarchitectureandchromatinlandscapeofthecorecircadianclockin mammals.Science.2012;338:349–354. O'Neill JS, Reddy AB. Circadian clocks in human red bloodcells.Nature.2011;469:498–503. O'Neill JS, van Ooijen G, Dixon LE, Troein C, Corellou F,BougetFY,etal.Circadianrhythmspersistwithouttranscriptionina eukaryote. Nature.2011;469:554–558.
5. Wang TA, Yu YV, Govindaiah G, Ye X, Artinian L, Coleman TP,et al. Circadian rhythm of redox state regulates excitability insuprachiasmaticnucleusneurons.Science.2012;337:839–842. MistlbergerRE.Neurobiologyoffoodanticipatorycircadianrhythms.Physi olBehav.2011;104:535–545.
6. DelezieJ,ChalletE.Interactionsbetweenmetabolismandcircadian clocks: reciprocal disturbances. Ann N Y Acad Sci.2011;1243:30–46.
7. Bron R, Furness JB. Rhythm of digestion: keeping time in thegastrointestinaltract.ClinExpPharmacolPhysiol.2009;36:1041– 1048.
8. HoogerwerfWA.Biologicclocksandthegut.CurrGastroenterolRep. 2006;8:353–359.

9. Konturek PC, Brzozowski T, Konturek SJ. Gut clock: implica-tion of circadian rhythms in the gastrointestinal tract. J PhysiolPharmacol.2011;62:139–150.

10. SchevingLA.Biologicalclocksandthedigestivesystem.Gastroenterology.2000;119:536–549.

11. Scheving LA, Russell WE. It's about time: clock genes unveiledinthegut.Gastroenterology.2007;133:1373–1376. PanX,HussainMM.Diurnalregulationofmicrosomaltriglyceridetransferproteinandplasmalipidlevels.JBiolChem. 2007;282:24707– 24719.

12. Pan X, Hussain MM. Clock is important for food and circadianregulation of macronutrient absorption inmice. J Lipid Res.2009;50:1800–1813.

13. Pan X, Zhang Y, Wang L, Hussain MM. Diurnal regulation ofMTP and plasma triglyceride by CLOCK is mediated by SHP.CellMetab.2010;12:174–186.

14. Sukumaran S, Almon RR, DuBois DC, Jusko WJ. Circadianrhythms in gene expression: Relationship to physiology, disease,drug disposition and drug action. Adv Drug Deliv Rev. 2010;62:904–917. Ando H, Yanagihara H, Sugimoto K, Hayashi Y, Tsuruoka S,Takamura T, et al. Daily rhythms of P-glycoprotein expressionin mice. Chronobiol Int. 2005;22:655–665.

15. Murakami Y, Higashi Y, Matsunaga N, Koyanagi S, Ohdo S.Circadianclock-controlledintestinalexpressionofthemulti-drug- resistance gene mdr1a in mice. Gastroenterology. 2008;135:1636–1644.

16. StearnsAT,BalakrishnanA,RhoadsDB,AshleySW,Tavakkolizadeh A. Diurnal rhythmicity in the transcription of jejunal drug transporters.JPharmacolSci.2008;108:144–148.

17. Musiek ES, Fitzgerald GA. Molecular clocks in pharmacology.HandbExp Pharmacol.2013;243–260. Xu C, Li CY, Kong AN. Induction of phase I, II and III drugmetabolism/transportbyxenobiotics.ArchPharmRes.2005;

18. Saedi E, Gheini MR, Faiz F, Arami MA (September 2016). "Diabetes mellitus and cognitive impairments". World Journal of Diabetes. 7 (17): 412–422. doi:10.4239/wjd.v7.i17.412. PMC 5027005. PMID 27660698. "Causes of Diabetes". National Institute of Diabetes and Digestive and Kidney Diseases. June 2014. Archived from the original on 2 February 2016. Retrieved 10 February 2016.

19. Heinrich J, Yang BY (January 2020). "Ambient air pollution and diabetes: a systematic review and meta-analysis". Environmental Research. 180: 108817. Bibcode:2020ER....180j8817Y. doi:10.1016/j.envres.2019.108817. PMID 31627156. S2CID 204787461. Retrieved 21 April 2022.

20. Ripsin CM, Kang H, Urban RJ (January 2009). "Management of blood glucose in type 2 diabetes mellitus" (PDF). American Family Physician. 79 (1): 29–36. PMID 19145963. Archived (PDF) from the original on 2013-05-05. Brutsaert EF (February 2017). "Drug Treatment of Diabetes Mellitus". MSDManuals.com. Retrieved 12 October 2018. "IDF DIABETES ATLAS Ninth Edition 2019" (PDF). www.diabetesatlas.org. Retrieved 18 May 2020. "Diabetes". World Health Organization. Retrieved 29 January 2023.

21. "Diabetes Mellitus (DM) - Hormonal and Metabolic Disorders". MSD Manual Consumer Version. Retrieved 1 October 2022. Shoback DG, Gardner D, eds. (2011). "Chapter 17". Greenspan's basic & clinical endocrinology (9th ed.). New York: McGraw- Hill Medical. ISBN 978-0-07-162243-1.

22. De Silva AP, De Silva SH, Haniffa R, Liyanage IK, Jayasinghe S, Katulanda P, et al. (April 2018). "Inequalities in the prevalence of diabetes mellitus and its risk factors in Sri Lanka: a lower middle income country". International Journal for Equity in Health. 17 (1): 45. doi:10.1186/s12939-018-0759-3. PMC 5905173. PMID 29665834.

23. Vos T, Flaxman AD, Naghavi M, Lozano R, Michaud C, Ezzati M, et al. (December 2012). "Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010". Lancet. 380 (9859): 2163–2196. doi:10.1016/S0140-6736(12)61729-2. PMC 6350784. PMID 23245607.

24. "The top 10 causes of death". www.who.int. Retrieved 18 May 2020.

25. Bommer C, Sagalova V, Heesemann E, Manne-Goehler J, Atun R, Bärnighausen T, et al. (May 2018). "Global Economic Burden of Diabetes in Adults: Projections From 2015 to 2030". Diabetes Care. 41 (5): 963–970. doi:10.2337/dc17-1962. PMID 29475843. S2CID 3538441.

26. Cooke DW, Plotnick L (November 2008). "Type 1 diabetes mellitus in pediatrics". Pediatrics in Review. 29 (11): 374–84, quiz 385. doi:10.1542/pir.29-11-374. PMID 18977856. S2CID 20528207.

27. "WHO | Diabetes mellitus". WHO. Archived from the original on June 11, 2004. Retrieved 2019-03-23.

28. Rockefeller JD (2015). Diabetes: Symptoms, Causes, Treatment and Prevention. ISBN 978-1-5146-0305-5.

29. Kenny C (April 2014). "When hypoglycemia is not obvious: diagnosing and treating under-recognized and undisclosed hypoglycemia". Primary Care Diabetes. 8 (1): 3–11. doi:10.1016/j.pcd.2013.09.002. PMID 24100231.

30. Verrotti A, Scaparrotta A, Olivieri C, Chiarelli F (December 2012). "Seizures and type 1 diabetes mellitus: current state of knowledge". European Journal of Endocrinology. 167 (6): 749–758. doi:10.1530/EJE-12-0699. PMID 22956556.

31. "Symptoms of Low Blood Sugar". WebMD. Archived from the original on 18 June 2016. Retrieved 29 June 2016.

32. "Glucagon–Injection side effects, medical uses, and drug interactions". MedicineNet. Retrieved 2018-02-05. "Diabetes - long-term effects". betterhealth.vic.gov.au.

33. Sarwar N, Gao P, Seshasai SR, Gobin R, Kaptoge S, Di Angelantonio E, et al. (June 2010). "Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies". Lancet. 375 (9733): 2215–2222. doi:10.1016/S0140-6736(10)60484-9. PMC 2904878. PMID 20609967.

34. O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, de Lemos JA, et al. (January 2013). "2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines". Circulation. 127 (4): e362–e425. doi:10.1161/CIR.0b013e3182742cf6. PMID 23247304.

35. Papatheodorou K, Banach M, Bekiari E, Rizzo M, Edmonds M (11 March 2018). "Complications of Diabetes 2017". Journal of Diabetes Research. 2018: 3086167. doi:10.1155/2018/3086167. PMC 5866895. PMID 29713648.