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IN THE CHRONOPHARMACOLOGY OF DRUGS AND MEDICINAL SUBSTANCES

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Annotation
Chronopharmacology of modern medicine is a science that varies in the pharmacological activity of different treatments on organic time and endogenous balance. It manages to check for rapid changes in the process of assimilation, distribution, digestion and elimination due to the timing of the treatment process. This knowledge aims to reach the system at the highest level of sensitivity and thus reduce the dose and minimize side effects. may lead to an improvement in reception time. Such application of chronopharmacology improves treatment with existing drugs.

Keywords: chronopharmacology, circadian, melatonin, chronotherapy, antidepressant, in vivo, circadian

In addition to taking into account the time-dependent pharmacokinetics of drugs to increase their effectiveness and reduce their side effects, i.e. chronopharmacology, targeted targeting of drugs affecting the circulatory system is an evolving and active field of pharmacology. Below are a few examples of recent advances in this area and discussed in detail elsewhere. Agomelatine is an antidepressant drug with melatonergic agonist and 5-HT receptor antagonist properties. Since both melatonin and serotonin are primary clock regulators and possibly secondary clocks, some of the antidepressant properties of agomelatin may mediate a re-synchronizing effect on circadian rhythms. In addition, physiological doses of melatonin stimulate the activity of several antioxidant enzymes. In the case of metabolic syndrome, such melatonergic compounds help to alter the sleep and wake cycle. As for the mechanism of clock genes, it is one of the rare circadian factors with known endogenous ligand (e.g., gem). Recently developed synthetic REV-ERB ligands have a significant effect on the expression of clock genes and have less pronounced reversible effects because they reduce nocturnal activity in mice instead of changing the sleep-wake cycle. Nevertheless, some of these promising compounds have been shown to improve the metabolic profile of obese mice. Other promising targets for the treatment of metabolic disorders are close members of the ROR family. Chronopharmacology is a science that differs in the pharmacological activity of different therapies over organic time and endogenous balance. Chronotherapy is a science that increases creativity and safety by balancing the fixation of prescriptions while synchronizing them with regular determinants of disease for 24 hours. Chronopharmacokinetics again controls the timing and predictable changes in the pharmacokinetic parameters of drugs. For example, it manages to check for rapid changes in the process of assimilation, distribution, digestion, and elimination due to treatment planning time. Psychoactive drugs - changes of more than 24 hours are not insignificant and in most cases the pharmacologist is provided with a different substrate for drug use at different times of the day. This knowledge can lead to the goal of reaching the system with the highest level of sensitivity and thereby improving the timing of medication

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administration to reduce the dose and minimize side effects. Such application of chronopharmacology improves treatment with existing drugs. Antidepressant drugs are subject to these general chronopharmacological considerations. It has also been found that common antidepressants or psychoactive medications can affect several aspects of circadian rhythms. The formulation of circadian hypotheses about affective disorders has led researchers to test the possible circadian effects of mood-stabilizing and antidepressant medications. Since the study of lithium introduced into plants, an important set of studies has been developed showing that psychopharmacological agents, including monoamine oxidase inhibitor corgilin, methamphetamine, and benzodiazepines, can alter the phase, period, or amplitude of circadian oscillations in many organisms. Most of the mixtures tested to date tend to delay the vinegar phase and prolong the life. However, the potential effects on mammalian pacemakers have not been fully investigated. Although the main site of circadian effects is the circadian pacemaker in SCN, these drugs can act at multiple loci. In particular, as mentioned above, all drugs alter the processing of light stimuli in the retina. Thus, many antidepressants alter circadian time or the body's sensitivity to light through actions in the central nervous system, and some have been shown to act on the SCN in a secondary visual pathway, through the lateral geniculation nucleus. Methamphetamine, in addition, acts as a pacemaker that speeds up eating. Improved mechanical knowledge for chrono-drug discovery Circulatory pacemaker in suprachiasmatic nuclei (SCN) and peripheral organs affects many biological processes, including circadian rhythm. Circadian rhythms are controlled by a circadian clock system consisting of cell-autonomous, self-sustaining molecular oscillators. The core of positive regulators (CLOCK, BMAL1, RORs) and negative regulators (PERIODs, CRYTOCHROMEs, REV-ERBs) and the secondary, stabilizing cycle form an interconnected transcription-translation negative feedback cycle. Disorders of circadian rhythms are associated with a variety of pathogenic conditions such as cancer, metabolic syndrome, cardiovascular disease, sleep disorders, and depression. Studies in Viennese workers and mouse circadian disorder models have identified the pathophysiological effects of clock regulation. Clock genes control many circadian rhythms associated with physiology and disease symptoms. Chronopharmacology is especially important when the risk or intensity of disease symptoms changes approximately over time. Chronopharmacology is a long-standing subdiplinate that recognizes the circadian effects of drug handling and efficacy. The efficacy and toxicity of some drugs vary depending on the dosing time. Chronotherapy tools are aimed at preventing or treating diseases by synchronizing medications to the patient's circadian rhythm to minimize toxicity or adverse effects and maximize efficacy. For example, "administration time" is important, as studies reviewing the 30 most commonly prescribed medications in Australia have proven convincing. Of the 27 available studies, 14 were found to have different therapeutic effects depending on the time of administration. Another interesting example of the complexity of chronotherapy is the dosage of synthetic oral glucocorticoids recommended for the treatment of asthma, to minimize sleep disturbances, including adverse effects. Similarly, the tolerability and efficacy of anticancer drugs such as irinotecan, 5-FU, and oxaliplatin are strictly regulated by circadian changes, as shown in both mice and human cancer patients. Overall, studies have identified an important role in changes in drug rhythm depending on the therapeutic outcome and

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safety of dosing time. However, chronotherapy remains on the edge of pre-clinical drug development programs, especially in in vitro testing systems. In vivo experiments have allowed the discovery of clock genes that regulate circadian locomotor activity rhythms using mutant animals, mainly drosophila, hamsters, or mice, which has led to insights into how clock function and disease symptoms and drug effects are affected. Recent studies in laboratory rodents have shown that circadian vibrations in physiological functions affect drug disposition based on a dose-dependent change in pharmacokinetics. However, using data collected from nocturnal rodents, it is difficult to predict circadian changes in drug pharmacokinetics in a diurnal human. Therefore, kinomolgus monkeys, as diurnal active animals, are used to assess the dependence of intestinal expression of P-glycoprotein on the dosing time of the pharmacokinetics of its substrates. Intestinal absorption of quinidine and etoposide of P-gp substrates was suppressed by the use of drugs on days when P-gp levels were high. Detection of circadian factors affecting drug absorption using monkeys may improve the approximate accuracy of pharmacokinetics for humans. The timing of dapagliflozin uptake, a selective sodium-glucose transporter 2, was tested using mouse models produced in a high-fat diet (HFD). Dapagliflozin administration in the light phase significantly reduced plasma glucose levels, insulin levels, fat adipokines, and adipocyte volume. On the contrary, these parameters remained unchanged in mice treated in the dark phase . In addition to studying dosing time, animal-oriented models, especially mouse models, have been widely used to test clock-oriented combinations. REV-ERBa (NR1D1) is a circadian clock component that functions as a transcriptional repressor. Recent years of research reveals a very wide role of REV-ERBa in pathological conditions, including local inflammatory diseases, heart failure and cancer. The REV-ERBa pulmonary clock was found to be important for IMM, which connects the transient threshold with the innate immuneitet and determines the amplitude of the effect on the visualised endotoxin. However, most of the studies conducted in vivo did not show 24-hour patterns that correspond to observations in human diseases. It is worth noting that the presence of circadian vibrations in the gene expression in a single cell, therefore, the presence of a cell-autonomous and self-sustaining oscillator was used system of correspondents Bmal1-luciferase and PERIOD-luciferase expression. The central circadian rhythm is maintained by neurons of supraciasmatic nuclei in primary cultures. Under normal culture conditions, (humidity, 37 ° C, 5-7% CO2), the newly exploited peripheral cells store the chaotic exertion of the clock genes for 12-14 hours, and maintain loose coordinated vibration patterns of the clock components. The cell in the cults can be synchronized with the physico-chemical instructions, for example, thermal vibrations, short-term exposure to a highly concentrated serum or a single medium exchange, in order to resume the molecular vibration of the clock genes, but due to different internal circadian cycles, their phase is gradually separated and randomly distributed. The recent concession proposed by Jean-Mishel Fustin and his colleagues highlights a huge deficit, especially in vitro conditions, because of the absence of cells used in such conditions, or impaired circadian action. . They also discuss the technical challenges that must be met to achieve the chip in one go, and the physiologically compatible protokols that bring out the stagnation of circadian behavior in cell culture systems improve the estimated value. In the treatment of metabolism-related genes and chemicals, it has been suggested that the corresponding enzymatic activity of different test cell lines has been significantly improved in the

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synchronized cells of the circadian and that the circadian rhythm is synchronized on the basis of Cell Culture, indicating compliance with the technique of expression of the rhythm. The Test system can improve the physiological significance of the corresponding in vitro model. We support the paradigm shift in pre-clinical studies by using the knowledge of sirkadian to develop appropriate, therapeutic measures, taking into account dorivor kinetics and the purpose and the circadian state of the disease. So now is the time when circadian factors become an integral part of Translation Research.

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