Chapter

Trending Advancements in Technologies Pertinent to Therapeutical Pharmacodynamics

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Abstract

It is omniscient that pharmacodynamics of a drug is understood as its effect on body by interacting with the structure of targets to either activate or inhibit their function/action. Based on the activity of the drug to the target binding site they have been classified into different types. Physiological, cellular, molecular, biochemical, and toxicological effects individually have a significant role in drug's effect and response. The mechanism of action, dosage and its response, therapeutic index are some of the noteworthy parameters to be considered in drug pharmacodynamics. This chapter comprehends the above-mentioned concepts, their importance in pharmacodynamics of drug, and the impact of recently developed methods like genome-wide or transcriptome-wide sequencing, chronopharmacodynamics, systems biology, pharmacometabolomics, etc., in different stages of drug discovery process, and how the digitization of therapeutics and healthcare direct the path to personalized medicine. The integration of bioinformatics, systems biology, and big data related approaches like ML & AI with the pharmacological (PK/PD) study highly benefits the patients' therapeutics.

Keywords: drug response, pharmacodynamic parameters, integrated approaches, pharmacology, digital therapeutics

1. Introduction

Pharmacodynamics (PD) elucidates the relationship of drug's concentration with the body (target), the way it affects and the impact it creates. It can be an ultimate characteristic feature to determine the effects exhibited by the concentration of the drug so as to assure its efficacy and safety. This feature in turn helps to avoid the adverse and toxic reactions caused by the drug that is administered to the body. PD forms a part of pharmacology that deals with the concepts of drug's interaction with any one of the four primary groups of target proteins, namely, ion channels, enzymes,

membrane carriers, and receptors, and concentration of drug with respect to time, and the effect caused by the dosage of the drug. Since, the concentration of drug is significantly related to the drug's effect, there are some parameters to confine its efficiency and some advanced computer-based techniques to highlight the concerns in this regard. These kinds of techniques enable PD to unlock the problems occurring while designing a novel drug which could be rectified by the development of precision making medicines through digital therapeutics/treatment. This in-turn paves way for PD to place its remarkable contribution in the phase of personalized medicine design based on the individual's requirement.

This chapter mainly focuses on the advanced technologies in today's trend in order to exemplify the crucial part of drug's PD characteristics in drug discovery process in consideration to human health and also, some of the basic concepts need to be taken into mind, like its importance in drug discovery process and the technologies which escalate the identification of PD of a drug are discussed in brief.

2. Parameters of pharamacodynamics

Parameters of PD illustrate the mode of action/interaction of the drug in the active site of the target. It is important that the drug should meet the PD parameters of concentration to inhibit the function of the target [1]. The drug responses can be manifested by the PD parameters.

2.1 Mechanism of action

Mechanism of action (MoA) is simply a biochemical interaction resulted in physiological response. This mechanism is enacted by the process called signal transduction which provides the description of the drug's (chemical) action (i.e. transmission of signal (chemical/drug) from the surface of the cell to the cytoplasm and/or nucleus of the cell) in the body/cell/receptor. At the beginning of this process, the cell recognizes the signal that bound to the receptor which is embedded either in the plasma membrane or present in the intracellular region. Transduction of signal takes place in the mid-way of the signal transduction process. Here the multi-step pathway utilized to carry out the rapid transmission of signal to the series of molecules. Protein kinases and protein phosphatases are the enzymes, trigger the phosphorylation cascade, and dephosphorylation processes in respect to activate and deactivate the protein. As a result of this, the secondary messengers transmit the signals brought from the cell surface receptor to the intracellular receptor to exhibit the cellular response by making changes in gene regulation processes.

Traditional methods (Direct approach) like affinity chromatography, and modern "omics" related high throughput methods (Indirect approach) are aid to identify the drug's mode of action by comparing the diseased cell (i. e., cell treated with the drug) with the normal cell [2]. The determination of MoA of a drug advantages in the categorization of the patients who are all exposing the similar kind of response to the treatment and estimation of accurate dosage of the drug can be done by monitoring the patients' target pathway [3].

2.1.1 Grouping of drugs based on mode of action

The signal transduction process allows us to group the drugs based on their binding mode and effects (either positive or negative). In general, drugs (ligands)

can be grouped into two (i) Agonist, and (ii) Antagonist. *Agonist* is a kind of drug that imitates the ligand embedded within the receptor structure that exhibits positive effect and produces biological response by activating the receptor in the signal transduction process. In simple words, it tends to replicate the expected (positive) reaction. More or less agonists possess the ability to meet up the maximum response by partially engrossing the receptors.

There are four different kinds of agonists lie under a single umbrella. The first type is the *full agonist* that means, it causes maximum amount of biological effect at maximum concentration. The second type is the *partial agonist,* that causes less maximum effect and therefore it receives partial response from the activation of receptor. The third type is an *inverse agonist* that binds with the receptor which is already in active state to minimize its activity. The fourth type of agonist is the *biased agonist* which makes the receptor capable of giving signals with various efficacies in their multiple downstream pathways.

Antagonist is another kind of drug that has no intrinsic activity in the receptor to produce any response. It prevents the agonist to bind at the receptor binding site by its increased concentration and reduces the fractional occupancy of the drug [4]. It forms a number of irreversible covalent bonds that will elongate the pharmacological activity [5].

There are two types of pharmacologic antagonist viz. *Competitive antagonists*, as its name says battle with the agonist to bind in the same active site of the receptor. *Non-competitive antagonists* lower the capacity of an agonist in its response towards the irreversible binding of the antagonist to the receptor. It produces a large antagonistic effect as an outcome [6].

2.2 Dosage and its response

PD encourages the utilization of several mathematical models namely, fixed effect model, logarithmic model, E_{max} model, and sigmoid E_{max} model [6] to explain the PD parameters such as efficacy (E_{max}), potency (EC_{50}), equilibrium rate constant (K), and sigmoidicity constant (n). These PD parameters can feature the drug-target interaction and their effect in the magnitude and duration of drug response. Rashed [7] estimated the magnitude and duration of response by comparing the maximum observed effect (MOE) to a sequence of doses and he also estimated the time taken for the half-life effect at various concentrations.

Efficacy (E_{max}) is the maximum response caused by the drug that evaluates the relationship between concentration and effect. *Potency* (EC_{50}) is the concentration of the drug at a stationary state which shows the half of the maximum effect. When the potency increases, the response from the respective concentration will decrease. This depends on some properties such as the receptor density, efficiency of stimulus–response mechanisms which is in use, drug affinity, and drug efficacy denoted in terms of EC_{50}/ED_{50}/Kd [6]. The hill coefficient (g) is an empiric parameter derived from the sigmoidicity of the effect-concentration correlation which defines the relationship between drug concentration and its effect. The hill coefficient value of >2 indicates a steep relationship, >3 indicates that it can be either all or none effect. The sigmoidicity constant (n) is a linear relationship of concentration-effect profile. The relationship between n and effect is inversely proportional (i.e.,) the increase in will decrease the concentration.

Affinity of a drug is also one of a parameter to be concern, defined by the time course and strength of binding of the drug with its target at certain degree of

concentration and it falls under the factors which are essential to determine the potency of a drug [5].

Some other parameters to be considered in PD are drug dissociation (Kd), receptor occupancy, up and down regulation of receptor. The *drug dissociation* (Kd) value shows how strongly the drug binds to its receptor for example, if the Kd value obtain from analysis is low, it is the indication of strong binding and higher affinity of a drug. The fundamental of *receptor occupancy* lies in the law of mass action, which says that an excellent PD response can only be attained if the number of receptors covered by the drug is more. The *up and down regulations of receptor* have been happened due to the long-time subjection of a receptor to an antagonist and/or an agonist [8].

2.3 Therapeutic index

The therapeutic index (TI) is one of the parameters help to determine and optimize safety and efficacy of the drug. It can be referred as the ratio of the drug's dosage at which the drug attains the no toxicity state [9]. It differentiates the drug effect caused at a particular concentration of blood from the amount of the effect that causes toxicity [10]. TI is the composition of drug effect (ED_{50}), toxic effect (TD_{50}), and lethal effect (LD_{50}). ED_{50} can be define as a scale of the concentration at which the half percent (50%) of patients exhibiting a particular pharmacologic effect. TD_{50} the amount of dosage needed to exhibit a particular toxic effect. LD_{50} is the prediction of the amount of dosage used to kill 50% of patients.

3. Role of pharmacodynamics IN DRUG'S effect and response

In basic, PD can be denoted as the determination of the effect of pharmacology and toxicology of the drug that appears as a result of the interaction occurred between the drug and receptor [11]. An individual drug's response to the target could be knocked off by the activities such as activation, inhibition of the targets' disease mechanisms at the active site described quantitatively with the support of PD. Depending on the activity of target and its biochemical pathway, the PD effects can be classified as direct, indirect, immediate, and delayed effects. The direct effect takes place in biochemical interaction pathway and the indirect effect occurs far from the end of the biochemical pathway.

With the knowledge of the drug concentration at the active site of the receptor, we can quantify the intense of the drug's effect and the magnitude of the response that is differing for the drug with the same concentration due to the disease and/or pre-administered drug. The response could be interrupted by many criteria such as the density of receptor on cell surface, signal transmission, and some regulatory factors.

The apparent effects such as physiological, cellular, molecular, biochemical and toxicological effects are the products of the drug-receptor interaction that is significant to make decision about dosage/concentration of the drug. Respective to the response of the drug action, the distribution and dosage of the drug increases simultaneously [8].

3.1 Physiological effects

Physiological factors like body type, quantitative amount of drug action, time course of drug action to the target, produces the effect that could interrupt the actual

behavior of the drug. Age is one of the significant physiological factors affecting the drug's action. When fixing the dosage of the drug, the age of the patients is necessary to be taken into account because, the absorption and distribution of the drug dosage requires more attention than the binding site of target. This is the reason why clinical trials mostly involve the middle and old age patients. Next to age, specificity becomes an important physiological factor affecting the drug's effect and response. The drug and the target should be very specific to provide successful results, otherwise it may lead to fatal results and hence, accuracy of monitoring is very much important. Another physiological factor to be considered is the time duration which can be defined as either at which time the drug enters the body or the time the drug reaches the target and at which time it's being excreted [12].

3.2 Cellular effects

Cell has been serves as a medium in which the interaction of drug and target takes place. There is a possibility for the occurrence of two different instances, such as, the bonding of drug with the target makes it function properly as a metabolite and the other one is, it forms a group of toxic compounds which exhibit toxicological effects as an end product. It is through the process of endocytosis, the drug enters into the cell surface area. The drug needs to be a lipophilic component, since the cellular membrane is made up of lipid bilayer, which permits only the lipophilic components and cause the cytochrome P450 to produce the inhibition action/to simulate the production of the factors which cause disease, thereby describing the effect and functioning of a drug.

3.3 Molecular effects

Drug by interacting with the macromolecules of the cellular organelles like, proteins, lipids, etc. causes some changes in the rate or magnitude of an intrinsic cellular response without producing any new responses. Many drugs that have been interacting with receptors (e.g., serum albumin) within the body do not cause any biochemical or physiological response directly even though some positive and negative effects like agonism and antagonism are stimulated by the action of the drug to the receptor. The understanding of drug interactions at the molecular level guides us to know about drug's effect in detail, and hence the dosage and distribution of the drug.

3.4 Biochemical effects

The biochemical effects, also an outcome of the drug-receptor interaction that is referred as therapeutic processing of drugs that aids the modification of the drug's conformation according to the environment of the receptor. Since the function of the molecule is associated with the structure of molecule, if the structure of the molecule is modified, then mechanism of receptor might be modified or inhibited by the instance of biochemical interaction which as a result exposes biochemical effects. The administration of oral drug creates a long lasting intense effect whereas the injections possesses and intense effects [13].

3.5 Toxicological effects

Toxicity referred as the production of toxic effect that is due to the entry of the xenobiotic components which are external chemical substances for humans/animals

that alter the function of the administered drug. Instead, there is a theory in the name of 'Darwinian toxicology' that shows the contrast view on toxicological effects by stating that these effects are the body's protective response against the drug has been administered to the body [14].

The detection of toxicological effects remains as a complex issue. It is even yet difficult to solve the toxic effects of drugs which are being subjected to the clinical trials. Perhaps, the drug passes all the pre and post drug designing/discovery stages by exhibiting positive results till the end of the clinical trials, it may become a huge problematic situation if it shows toxic effects after marketing the drug. It is inevitable to repeat the process again from the start point. This shows the importance of understanding the behavior of the drug molecule at the molecular level to avoid such toxicological effects. One of the "omics" concepts, biomarker identification helps to screen drugs with its associated toxic effect.

There are five different toxicity conditions, the first one being "On-target" that is the mechanism-based toxicity caused due to the interaction of drug with the same target to produce required pharmacological response. The second one is "Hypersensitivity" and "Immune response". The third one is "Off-target" toxicity, in which the drug interacts with alternate target and causes toxicity. The fourth one is "Bioactivation", which converts multiple drugs as product of metabolites (reactive). These elements manipulate and being a starting point of toxicity of the proteins that has to be avoided. The fifth condition is an unfamiliar condition named as "Idiosyncratic reactions" known as troublesome responses [15].

4. The impact of recently developed methods over pharmacodynmics approaches

4.1 Genome-wide association studies (GWAS)

Genome-wide association studies (GWAS) act as a tool to identify the position of the gene that affects the drug susceptibility and response to the body. The genomic variants cause the PD-PGx effects with respective to the variations in patient response in the pathways of drug-target interaction. Whole genome sequencing helps to determine the PGx markers exhibiting distinct features by employing conventional genetic screening [16].

The genetic architecture of drug response can be described in deep by incorporating the PD process with GWAS. This permits to find out the genetic influences regarding the drug response and adverse drug reactions through computational tools using the mathematical equation and statistical method [17].

In this regard, candidate-gene studies offer data on the cases that may vary from adverse drug reactions to the single gene's alleles. Some victorious examples speak about and suggest this approach for the drug toxicity investigation, interpretation of drug-response. The response for a drug might be differing from patient to patient because they may not respond properly for a particular drug or it may need an error-free dosage to acquire good results. Phase III of clinical trials adopts GWAS to determine the best drug with a precise dose [18].

4.2 Chronopharmacodynamics

Chronopharmacology is a field which depends on the biological time and endogenous periodicities to discern the drugs' biochemical and physiological effects on body,

drug action mechanisms, drug-concentration relationship, and impact of circadian clock to the effect of the drug. Circadian clock has established its role in regulatory metabolism, detoxification, and few other physiological processes.

Chronopharmacodynamics validates the changes of circadian in the drugs' mode of action to provide optimized pharmacodynamic response. Chronotherapeutics deals with the scientific approach of synchronizing drug delivery with the body's circadian rhythm, to maximize the therapeutic index and enhance effectiveness. Studies have revealed that a drug may have different effects depending on the time of dosage [19].

Circadian pharmacodynamics/Chronesthesy could be a variation associated with time effects that allow some modifications in treatment to improve the chances of efficacy and safety and to lower the side effects of drug. However, side effects of drugs are influenced by physio-chemical properties and PK/PD of the drug. Since, circadian variation affect the PD, it becomes essential to consider the circadian rhythm prior to drug administration so as to prevent the timely variations that occur in the drug's MoA [20].

4.3 Systems biology

Systems biology sets a trend of using data mining and statistical tools which aid to analyze the networks to locate the topology of biological systems and to build dynamic ordinary differential equation (ODE) models to represent the mechanisms of biochemical reaction. Systems pharmacology has evolved as a discipline that possesses the features of both systems biology and pharmacology that could be employed in all the phases of drug research and development. The enhanced PD (ePD) models highlight the importance of testing the drug effects in a multilevel network and the treatment of an individual patient to promote accuracy and benefits of clinical decision-making [21]. It integratively employs various domains such as systems engineering, systems biology, and PK/PD which enhances the understanding of the complex biological systems by iterating the computation and mathematical model construction, experiments and quantitatively analyzing different interactions that occur between drug and biological systems [22].

The Network-based Systems Pharmacology is an impactful way to understand the adverse effects of drug. It benefits by increasing the drug efficacy, regulating signaling pathway with multiple channels, and provide higher success rate of clinical trials, and also lowering the costs of drug discovery and development [6].

4.4 Pharmacometabolomics

Pharmacometabolomics (PMx) related studies have turned their concentration towards the areas such as biomarker identification and metabolic patterns. PMx also known as Pharmacometabonomics, is a recently developed discipline that puts in together different aspects of an individual's metabolite profile via metabolic approaches and predicts the individual's variation with respect to drug response phenotypes. It paves a way to identify endogenic metabolites and their associated pathways, individual drug PK/PD characteristic predictions and biomarkers for observing disease progression.

Metabotype (an individual metabolic profile) is one of a new strategy that consists of baseline metabotype and treatment metabotype. *Baseline metabotype* can be obtained from pre-dose sample which deals with the heterogenic data and subtypes of disease. *Treatment metabotype* are obtained from the samples which are collected while dosing in order to determine the effect/side effects of drug and changes in response

exhibited in molecular pathways. These two metabotypes help to find the variation occurred due to the effect of drug and that is exposed by inter and intra-patients. The investigation of therapeutic responses depends on these two metabotypes and the metabolic signatures that help to build models of patient's response to drug.

Another strategy is the PMx based biomarker identification which involves the steps such as data collection, process, statistical analysis, and biochemical interpretation. The biomarkers identified as an end-product of the PMx procedure may act effectively for responders and safely for non-responders in addition to some other unfavorable action and they are used to fix the range of drug dosage based on the metabolites discovered from treatment samples. PMx also identifies biomarkers involved in the downstream effects of pathophysiology and PD/PK events [11].

4.5 Artificial intelligence (AI)

AI speeds up the validation and optimization of the target and the drug structure respectively. AI approaches have been employed to check the safety and efficacy of the drug molecules by developing and analyzing big data.

Recently, QSAR approaches have also been transformed as AI-dependent QSAR approaches, namely, linear discriminant analysis (LDA), support vector machines (SVM), random forest (RF), decision trees (DT) and so on. The nearest-neighbor classifier, RF, extreme learning machines, SVMS, and deep neural networks (DNNs) are able to predict the *in vivo* activity and toxicity, physicochemical properties and bioactivity of the developed drugs. With the usage of training data set (n number of compounds), predictive models have been developed and tested to predict the properties of the data (n number of compounds lesser than training data set) based on some parameters such as molecular surface area, molecular mass, total hydrogen count, refractivity, volume, logP, total polar surface area, sum of E-states indices, solubility index (log S), and rotatable bonds. By choosing anyone of the drug feature and its respective target, AI can predict the binding affinity of the drug to its target. Tools designed based on ML and DL approaches such as KronRLS, SimBoost, DeepDTA, and PADME are used to determine drug-target binding affinity. DL-based methods like DeepDTA, PADME, WideDTA and Deep Affinity produce better results when compared to the ML-based methods via the application of network-based methods [23].

Deep learning (DL) models surpassing the PK/PD methods are being followed in the clinical trials to predict the time course of the response for the respective dose of the administered therapeutic. This requires quite a lot man power to model the dynamic systems for the bulk amount of data to produce the best product (drug).

The integration of major concepts with deep learning workflow may provide an effective outcome. The models which are built with the combination of machine and human support gain a center role in the diagnostic procedures to monitor the real time treatment data. The deep learning and PK/PD approach together help to meet the necessities of automatic modeling to define the dosage by reducing the amount of time and human energy has been spent.

AI and ML system is used to detect and predict the data of individuals' symptom by means of feedback loop using digital biomarkers thereby leading to precision medicine. Certain companies involving the AI robots combined with psychological models in therapeutic areas. Some other companies design pills with an ingestible mini sized sensor coated with copper and magnesium on alternate side. Once the pill is administered to a person (patient), it will pair the two sides and start to generate

signal for the wearable sensor patch. The person who worn the sensor patch may get a digital record via a mobile app with the permission of his/her doctor (healthcare provider). The sensor patch will monitor the persons' activity, heart rate, sleep quality, temperature and even monitors disease conditions like diabetes, hypertension, etc.

Although AI is a boon for the pharmacological area, it has some notable limitations in handling data, such as its range, growth, variability, and unpredictability. The future of AI in clinical pharmacology has been expected to predict the concentration and effect of the drug with the help of DL models which could be implemented in digital devices that aid to monitor the treatment data automatically [24].

5. Digitized therapeutics and healthcare IN personalized medicine

Personalized medication become robust by predicting the accurate treatment results for the drug which will administer in the live environment and the high-throughput measurement of bio-molecules (genes, proteins, and metabolites) present in a cell. To fulfill this criterion, currently emerging technologies of digital health provides the capability to evaluate the patient's response to the drug in the real world and time by converting therapeutics as a Digital Personalized Medicine (DPM).

The Internet of Things (IoT), a network-based technology provides support in this regard. The Internet of Pharmaceutical Things (IoPT) digitally quantifies the effects of drug in real-time PD and enables remote monitoring [25]. Sensors and wireless connections are used to capture drug interaction and phenotype data. For example, Digital twin concept is used to improve diagnostics and treatments. Digital twins are an assembly of unlimited copies of models of all phenotypic, molecular, and environmental factors related to disease mechanisms. Each twin is treated computationally with potential drugs and a drug with high effectiveness is selected for treatment [26].

Personalized drug delivery system (PPDS) is a constant measurement of dosage that incorporates the Active Pharmaceutical Ingredients (APIs) with patient-adopted precise dose and possesses different aspects that could be modified to enhance the drug identification, absorbability, excretion and monitoring the treatment. The incorporation of PDDS and Digital health is the current upcoming area that may aid to upgrade the healthcare systems, cost-efficient treatments and boost the result of overall healthcare [27].

Digital health is a merge of diverse platforms and systems which offer solutions based on technologies to improve healthcare. This comprises almost all the technologies that are responsible for patients' health and the concepts such as mobile health (mHealth), telehealth (telemedicine), smart devices, sensors and wearables, health information technology and personalized medicine.

Digital therapeutics (DTx) is one such category of digital health solutions that provides evidence-based, software-driven therapeutic interventions for the prevention and management of medical disorders or diseases that aims to reduce the consumption level of pharmaceuticals or to be drug-free under certain conditions. It serves as an indicator to analyze drug effectiveness and is also used to compute the response of a person to a drug which is under investigation in clinical trials.

Products (digital therapeutics) developed by the implementation of advanced technology have to be approved by regulators and they should follow certain principles which are categorized based on the medical purpose provided by Digital Therapeutic Alliance (DTA) to serve individuals with safe and effective treatment. Criteria like, growth of digital analytical tools, up-gradation of data visualization and

machine learning encourage researchers to convert data as knowledge that will assist clinical decision-making [28].

Nowadays the term "E-patient", pioneered by Dr. Tom Ferguson in 1999, has been gaining attention, representing the patients who are all able to decide their own health and healthcare and capable of making health-related decision utilizing the technology. They are developed to treat/manage/prevent certain disease conditions including chronic diseases. With the help of DTx, physicians can treat their patients residing anywhere and anytime beyond the border of a clinic or a hospital. It helps them to make accurate diagnostic decisions at the right time with the concern about patient care. This ideology proceeds towards the personalized treatment of the patient through monitoring and tracking the response for the prescribed therapies [29].

6. Conclusion

Development of drug is a multistep process that deals with multiple concepts and domains. It requires a holistic knowledge of all related areas to identify a potential drug to provide an expected result. The drug begins its action from administration to excretion from the body. The prediction of drug's action in human body/cell is essential to develop a potent drug with no toxic effects. This can be accomplished by the already developed/developing computational approaches with the insight of the PD associated concepts like parameters to consider, and the relative effect and response of the drug.

This opens up the door of personalized medicines in the form of digital therapeutics, enable the physician to prescribe medication on the basis of patients' requirement. But it is still important to test and mining evidences in order to evaluate its efficacy and safety.

This chapter helped us to realize that the computational approaches discussed in this chapter are providing such good outcomes when combining them with one another. Even though, PD has attained a remarkable place in the drug discovery and marketing, an effective product (drug) can be obtain by unifying the PK/PD properties of a drug. In other words, as a whole pharmacology of a drug should be taken into concern in order to design a patient-friendly drug/medicine.

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