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Pharmacokinetic Modeling: Target for Antidepressant Drug Development

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Abstract

Targeting the nicotinic acetylcholine receptor is a crucial new direction in the development of antidepressant drugs (nAChR). This receptor, which is extensively distributed in the areas of the brain connected to depression, is also involved in other significant processes that are connected to depression, including stress and inflammation. Mecamylamine- and cytisine-based compounds can be used as a general classification of the two types of medications that target nAChRs. Strong preclinical outcomes support the antidepressant efficacy of both classes when used in conjunction with other primary antidepressants, and these medications likely exert their effects by antagonistically binding to nAChRs at the 42 position (e.g., monoamine reuptake inhibitors). Preliminary findings in this field provide a compelling case for further investigation of the nAChR as a target for the creation of new antidepressant medications, despite the paucity of clinical evidence in this domain. Physiologically based pharmacokinetic (PBPK) modelling is a concept that has been around for a while, although it has not seen much use. The rise in the number of papers in this area, however, indicates that both interest in and use of this modelling technique has grown. The technique, uses, and restrictions of PBPK modelling are briefly illustrated in this work, with a focus on the use of PBPK models in the development of paediatric medications. Several specific examples are also provided. Despite the fact that PBPK models do have significant drawbacks, the technique has a very high potential for success. In order to enhance decision-making during drug discovery, PBPK models can be used to examine drug pharmacokinetics in various physiological and pathological contexts or in various age groups. This is possibly most crucial.

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Introduction

One of the most prevalent mental illnesses in the world, depression has a major effect on public health. The fact that there are so many drugs accessible does not change the fact that many affected patients remain in pain. In the largest antidepressant comparative efficacy study, the Sequenced Treatment of Alternatives to Relieve Depression, roughly half of patients receiving initial treatment with antidepressants responded, but only a third reached remission, and up to a third never reached remission despite multiple trials of various medications and combinations [1]. A large majority of the antidepressants used in STAR*D directly increase synaptic availability of monoamines, frequently by inhibiting reuptake. It is obvious that we require new, more effective interventions with innovative modes of action. Future research into the development of antidepressant drugs, particularly those targeting the nicotinic acetylcholine receptor (nAChR) [2], shows great promise. The cholinergic theory of depression, which postulated that excessive cholinergic signalling can cause depressive symptoms, was advanced by studies from the 1970s, on which the nAChR literature is based. Due to concerns about the safety and tolerability of the chemicals available at the time, this field of research was largely abandoned [3]. Significant interest in the antidepressant characteristics of nAChR regulation has reemerged more recently as a result of the introduction of novel drugs that target this system. Building on earlier studies, this paper provides a review of the research on the use of nAChR modulators for the treatment of depression

their use for additional purposes, such smoking cessation and cognitive improvement, has already been covered elsewhere [4].

Physiologically based pharmacokinetic (PBPK) modelling is a concept that has been around for a while, but it hasn't received the attention or been used as much as it should. However, as shown by the sharp rise in publications in this area, interest in and application of this modelling technique have expanded during the previous few years [5]. Since PBPK models can link paediatric and adult pharmacology, the launch of the Pediatric Exclusivity Program in the United States and Europe may also help this modelling technique become more widely used. The basic idea behind PBPK modelling is to quantitatively characterise pertinent physiological, physicochemical, and biochemical processes that affect how a substance behaves pharmacokinetically in as much detail as is suitable or required [6]. To do this, concepts of physiology and anatomy are used to describe the species to be modelled as a structure made of physiologically relevant compartments, where each compartment frequently represents a particular organ or tissue [7]. The blood circulation loop connects these compartments, which follow the anatomical structure of the body. For each compartment, mass-balance equations that describe what happens to the substance inside are established. The PBPK model employs physiological and substance-specific factors to resolve these equations. In the end, PBPK models can describe and/or forecast drug pharmacokinetics in specific individuals or under specific physiological or pathological settings, with the main output of a simulation being a set of concentration-time curves illuminating the temporal behaviour of the drug in blood [8].

The Nicotinic Acetylcholine Receptor

NAChRs are functionally related to muscarinic acetylcholine receptors because of their shared capacity to react to acetylcholine binding (mAChRs). NAChRs, on the other hand, are ligand-gated ion channels with affinity for both nicotine and acetylcholine, in contrast to mAChRs, which activate ion channels via G-protein coupling. Membrane polarity and intracellular messenger cascades are impacted by the inflow of cations brought on by activated nAChRs. Although nAChRs are found in both the peripheral and central nervous systems, this article focuses on nAChRs in the CNS. Both high affinity and low affinity nAChRs are composed of five pentameric units. High-affinity nAChRs are heteromers of the - and -subunits, and they are inhibited by substances like dihydro-erythroidine and mecamylamine while being activated by modest dosages of the -subunit 42 partial agonist varenicline. The ventral tegmental area, locus coeruleus, and dorsal raphe nucleus are a few examples of brain regions with a high concentration of CNS nAChRs. The n-methyl-D-aspartate (NMDA) glutamatergic system and other neurotransmitter systems, particularly the dopamine system, are thought to be the principal targets of their activity. The hypothalamic-pituitary-adrenal axis is one of the numerous neurobiological systems that is dysregulated in depression and involves nAChRs. Since corticotropin-releasing factor (CRF) neurons have nAChRs on their presynaptic terminals, CRF release can be inhibited by nAChR antagonists. Similar to this, there is growing interest in how nAChRs may contribute to inflammation, which is related to depression. The 'cholinergic ascending anti-inflammatory route,' as it is known, is regulated by nAChRs.

Targeting nAChRs for Depression

The majority of studies targeting nAChRs for depression have concentrated on a number of parent substances and their derivatives. Mecamylamine, a non-specific nAChR antagonist, and the plant alkaloid cytisine, which has been studied for its actions on 42 nAChRs, are the two main substances that have been assessed thus far. The following parts are arranged by parent compound and begin with a discussion of the preclinical literature that supports use for depression. If any clinical data is available, it is then followed by that discussion.

Cytisine

From the seeds of the Cytisus labornum, cytisine is obtained. It is a partial agonist at the nAChR 42. In the 1950s, it was first created as a low-cost smoking cessation medication in nations that were once part of the Eastern Bloc, and it is still sold over-the-counter in Russia. Other pyridine-like compounds, including varenicline, dianicline, and sazetidine, are derived from it as its parent structure. In both acute and chronic rodent models, cytisine consistently showed effects that were similar to those of antidepressants. C-fos, a neuronal activity-reflecting immediate early gene transcription factor that downregulates in the context of persistent antidepressant treatment, has been associated to decreased expression after cytisine administration. Further highlighting the potential of this parent molecule are partial 42 nAChR agonists based on cytisine that also exhibit antidepressant-like effects.

Varenicline

In an effort to create new smoking cessation medications, varenicline was created from its parent molecule cytisine. It is a partial agonist at the high-affinity nAChR 42 and a full agonist at the nAChR 7. Varenicline generated modest antidepressant-like effects in preclinical mice during the FST that were comparable to those of the SSRI sertraline but less potent than those of the TCA amitriptyline. Varenicline did, though, considerably enhance FST performance when used in conjunction with sertraline. These outcomes were observed with lower varenicline dosages, indicating a dose-dependent outcome with an adverse outcome. However, varenicline was used in that trial as a monotherapy and the majority of the doses examined (0.01-1 mg/kg) were lower than those of other studies, which is why one more investigation concluded that the drug had no effect on the FST and TST.

Dianicline

For high-affinity 42 nAChRs, dianicline, which is likewise derived from cytisine, was created. Although it has very modest CNS penetration, dianicline has a preclinical profile that is comparable to that of varenicline in that it can influence dopamine release. No research examining this substance's impact on preclinical depression models exist as far as we are aware. The one clinical research that is currently available on dianicline for smoking cessation was unsuccessful, having little impact on smoking outcomes or depressive symptoms, as would be expected for a drug with poor CNS penetration.

General Model Structure Specification

The major organs and tissues are modelled in PBPK models as compartments that are connected by a blood circulation loop that is further separated into arterial and venous pools. These models mimic the structure of the live creature being researched. The available information on the anatomy and physiology of the biological system, from the cellular level to the entire body, serves as the natural basis for the selection of compartments. However, since the critical components of the drug's pharmacokinetic events must be assessed, this does not automatically determine how many bodily regions, or compartments, are required. The decision is also influenced by the goal of the model, as well as the modelled drug's physicochemical (binding, lipid solubility, and ionisation) and pharmacological (mechanism of transport, site[s] of action) characteristics. The specifics of the body's adipose tissues, for instance, are less crucial if the medicine is not lipid soluble. Similarly, if only the drug's absorption is necessary, a model that simply incorporates the organs or bodily tissues involved in the process of absorption may be adequate. However, because the main characteristics of drug distribution can frequently be described with models that have surprisingly few details, "lumping" is a common strategy in structuring PBPK models. This strategy increases the complexity of the models and the amount of information incorporated with an increase in the number of represented tissues. Compartmentation refers to the grouping of tissues that have comparable physiological, physicochemical, and biochemical characteristics.

Organs Model Specification

The model of each specific organ or tissue must then be specified (i.e., the subcompartments that represent each organ/tissue must be established). For each tissue or organ, one to four compartments are used in the great majority of PBPK models. The decision to compartmentalize is based on information already available on the kinetics of the drug once it enters the tissue and the biochemical process that takes place throughout that phase. Different assumptions made at this level should be distinguished from one another. The assumption used to assign a perfusion rate-limited tissue model is that the medication diffuses readily and quickly through membranes upon entry with blood circulation, without the need for diffusion barriers, and that the rate of blood supply is what is rate limiting. The more complex permeability rate-limited tissue model will be given with at least a two-compartment tissue structure if it is assumed that there are physiologically identifiable diffusion barriers to the distribution of a compound in the tissue, such as capillary membranes (such as the blood-brain barrier for some hydrophilic molecules) or cellular membranes, or both. In addition, a well-stirred model makes the assumption that there isn't a gradient in concentration inside a tissue or organ compartment. Contrast this with the dispersion model, in which concentration gradients still exist despite the inability to identify a diffusion barrier. Examples of a well-stirred, one-compartment tissue model with a perfusion rate limit and a permeability rate limit.

PBPK-Model Parameterization

The parameters of the model equations must be stated and approximated once they have been written. Physiological or substance-dependent parameters are typically included in PBPK models. The anatomical structure and physiological functions of the species being represented are described by physiological parameters, which include organ volumes, heart output and blood flows, tissue composition, surface area, pH levels, and/or gastrointestinal tract transit durations. It is known that the values of these parameters change with age, physiological state, and species and people. Despite the vast amount of literature that is currently accessible presenting such physiological data in a variety of species, particularly the ICRP's (International Committee on Radiological Protection) annals for human values for animal values. The second set of parameters required for a PBPK model vary on the compound and include details like permeability-surface area products (P*S) and the partitioning of the substance between body tissues and the blood (KpT). These parameters can either be derived via in vitro investigations, by extrapolating the experimental in vivo values from animals to people, or by estimation utilising particular algorithms. These methods are found in a large number of specialist PBPK modelling programmes, such as those created by Poulin and Theil, Rodgers and Rowland, etc.

Discussion

The architecturally unique nAChR-7, made up of five identical nAChR-7 subunits, has been studied for schizophrenia and cognitive impairments; although earlier research indicates that nAChR-7 agonists may also have antidepressant action. Studies from the late 1990s revealed that the SSRI fluoxetine needed to bind to 7 receptors in order to have antidepressant effects, and it is probable that agonism at this receptor contributes to the preclinical antidepressant-like effects of varenicline. Contradictory outcomes have been produced thus far by compounds that target this nAChR. When used in conjunction with other antidepressants, PNU-282987 has been demonstrated to exhibit effects similar to those of an antidepressant; however this has not been confirmed in subsequent investigations. Although the particular mice strains employed in these investigations might have been confusing. Despite PBPK modelling was initially developed in the pharmaceutical industry, it has many uses in environmental toxicology and risk assessment and has grown to be a generally accepted method. Although PBPK modelling is increasingly prominent in the realms of pharmacology and drug development, it can also be used for a number of other things. PBPK modelling can be used to predict the pharmacokinetics of potential drug candidates in animals even at the early stages of drug development programmes in the preclinical phase. This can reduce the need for superfluous animal testing and save a lot of time. Another illustration showed the value of a PBPK pharmacodynamics model in choosing the most promising chemical out of five possible clinical candidates. PBPK models have been frequently utilised for IVIVE of drug kinetics through diverse species or routes of administration because they include pertinent data from multiple sources, including those that are substance-dependent and physiologically relevant. The PBPK-modeling method has also come into its own as a teaching tool that can assist users in comprehending the impact of various procedures and/or variables involved in determining drug disposition and pharmacokinetic behaviour. Through the simulation of various

dosing regimens, PBPK-modeling is frequently used to describe and/or predict the pharmacokinetic profiles of drugs, enabling the evaluation and optimization of established therapies. It has also been used to characterise and/or forecast medication pharmacokinetics under various physiological and pathological circumstances, including as during pregnancy, during surgery, and in cases of liver cirrhosis. PBPK modelling has also been used to investigate the impacts of diet, ageing, rest and physical activity, and gender differences. A parent drug's and its metabolite's pharmacokinetics can be estimated using PBPK modelling, which has also been used successfully to predict the severity of complex drug-drug interactions and to explain how the pharmacokinetics of a drug change when another drug is administered concurrently. This information is crucial for the pharmaceutical industry because it helps to increase safety and lower the attrition rate of new drugs. A further benefit of PBPK models is that they make it possible to anticipate how a medicine or toxin would be absorbed into the body, not just in the plasma or blood but also in distant or inaccessible compartments like the brain or tumour tissues.

Conclusion

NAChRs are a good target for the creation of antidepressant medications, as is abundantly obvious. With the sazetidine-A outcomes indicating that the 2 component is required for antidepressant action, preclinical data show that drugs that target the 42 nAChR have the highest potential. When used in conjunction with other antidepressants and in small doses, all of these medications seem to be the most effective. According to the relatively few clinical studies that have been conducted so far, cytisine and dianicline are unlikely to be effective augmentation drugs, whereas varenicline may be, and mecamylamine shows promise. Future clinical trials should carefully take into account the fact that it is unclear whether these substances would work differently in populations that smoke or don't smoke. as well as the known restrictions of the readily available antidepressant drugs. This article offers a concise explanation of the PBPK modelling approach, applications, and limits. It pays particular attention to the use of PBPK models in the development of paediatric medications and presents some in-depth examples. The PBPK modelling technique offers a wide range of applications since it has the ability to be applied at many stages of drug development, from early discovery phases and preclinical development to clinical phase studies. In order to investigate the impact of various factors on drug pharmacokinetics, to address the magnitude of drug-drug interactions, and to help optimise the conduct of clinical trials in special populations like paediatrics, where ideal planning is required to reduce the ethical and technical challenges, simulations by PBPK models are developed. To improve the acceptance of these strategies in the planning stages of clinical trials or for the use of individual pharmacological therapy, prospective examples that guarantee the therapeutic value of such a modelling technique are necessary and crucial. There are drawbacks and flaws to PBPK models. For instance, some physiological systems are poorly described, and there may be information gaps, because they reflect current scientific knowledge. Additionally, the accuracy of the simulations is reliant on the relevant model and the data it incorporates, and the outcomes are tainted with uncertainty and prediction mistakes. The application of the PBPK modelling technique is still still somewhat widespread, but there are now numerous widely usable software solutions with more user-friendly interfaces that do not necessitate a thorough modelling.

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Conflicts of Interest

The author has no known conflicts of interested associated with this paper.

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