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Mohit Gupta
IIMT College of Medical Sciences, IIMT University, Meerut (U.P.)

Ravi Shekhar
Department of Pharmacy, Dr. Bhimrao Ambedkar University, Agra (U.P.)

Jagdish K Sahu
School of Pharmacy and Technology Management, SVKM'S NMIMS (Deemed to be University), Shirpur, Distt. – Dhule, Maharashtra

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Correspondence

Jagdish K Sahu
School of Pharmacy and Technology Management, SVKM'S NMIMS (Deemed to be University), Shirpur, Distt. – Dhule, Maharashtra

Email:
jagdish.pharmacist@gmail.com

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Role of Drug Discovery in Central Nervous System Disorders: An Overview

Mohit Gupta, Ravi Shekhar and Jagdish K Sahu

ABSTRACT

Central nervous system (CNS) stimulants are drugs, which produce a response that could be used to alleviate a particular medical condition. These are the agents, which speed up to treat conditions characterized by lack of adrenergic stimulation, including narcolepsy and neonatal apnea. The majority of CNS stimulants is chemically similar to the neurohormone norepinephrine and simulates the traditional "fight or flight" syndrome associated with sympathetic nervous system arousal. A small figure of added members of the CNS stimulant class do not fall into definite chemical groups. The review on central nervous system stimulants gives detail study of CNS stimulant drugs, their mechanism of action and *in vivo* models of CNS stimulants.

The brain is a delicate tissue, and advancement built very effective methods to guard it. Unfortunately, the same mechanisms that protect it against intrusive chemicals can also upset therapeutic interventions. Many current medications are rendered unsuccessful in the treatment of cerebral maladies due to our incapability to efficiently deliver and sustain them within the brain.

Keywords: CNS Stimulants, Blood brain barrier (BBB), Drug toxicity, Drug Safety,

1. INTRODUCTION

Central nervous system (CNS) stimulation is the primary action of a diverse group of pharmacological agents and side effects associated with the administration of larger group of drugs. Central nervous system (CNS) stimulants are agents that increase physical activity, mental alertness and attention span. Central nervous system stimulants are used to treat attention-deficit hyperactivity disorder and narcolepsy.

The blood-brain barrier (BBB) and its penetration by neurotherapeutics become much important. The ability to design drugs capable of penetrating the BBB and effecting the desired biological response is a tough challenge. On the other hand, peripherally acting drugs must to retain definite physical-chemical properties that prevent them from crossing the BBB.[1]

Generally, moderate lipophilic drugs cross the BBB by passive diffusion and the hydrogen bonding properties of drugs can significantly influence their CNS uptake profiles. Polar molecules are normally poor CNS agents unless they undergo active transport across the CNS. Size, ionization properties, and molecular flexibility are further issues detected to influence passage of an organic compound across the BBB. One of the main concerns of insufficient pharmacokinetics of both developmental and marketed drugs is failure in advanced development.[2-5]

Despite the significant changes in drug discovery, multiple classes of compounds affecting CNS processes at various steps are successfully used clinically, and many more are in development.[6]

Many neurodegenerative diseases, such as Alzheimer's and Parkinson's disease, are shocking disorders that affect millions of people worldwide. However, the number of therapeutic options remains severely limited with only the availability of symptomatic management therapies. With the better understanding of the pathogenesis of neurodegenerative diseases, discovery efforts for diseasemodifying drugs have increased dramatically in recent years. The task of finding new effective drugs targeting central nervous system (CNS) has unique challenges due to blood brain barrier (BBB).[7-10] Furthermore, the relatively slow progress of neurodegenerative disorders creates another level of difficulty, as clinical trials must be carried out for an extended period of time. This review is intended to provide molecular and cell biologists with working knowledge and resources on CNS drug discovery and development.

2. BLOOD-BRAIN BARRIER

The interface between the blood and an organ is mediated by endothelial cells that control the transfer of molecules from the blood stream into the cell and also from the cell to the blood. Basically, there are three methods of transfer for small molecules that can be classified according to whether there is an energy-requiring step. Two of these methods, passive and facilitated diffusion, are concentration determined and unidirectional rendering to the gradient.11 Facilitative diffusion is comparatively uncommon, but glucose is moved into the CNS by a non-energy-dependent glucose carrier. The third process, active transfer, requires an energy source (ATP) and can transfer molecules via a carrier against a gradient. In a global sense, the general requirements for passive and facilitated transport are common. However, depending on the organ, the epithelial cells can have differing specifics for allowing drugs to transfer from the blood to the cells in the organ. The CNS, being delicate to many compounds in the blood and also to drugs, is intended to be very selective in what is permitted in. As such, it is certainly an outlier as is verified by the lack of relationship between intestinal Caco-2 cell and BBB active efflux.[12]

The cause the BBB is an outlier is that BBB epithelial cells form tight junctions that efficiently preclude paracellular diffusion. In addition, the cells possess few pinocytotic vesicles and lack fenestration. Therefore, BBB transfer is through transcellular diffusion through the membranes. A drug undertaking transcellular diffusion can be metabolized by a challenging cordless of metabolic enzymes. For example, decarboxylation of 3-(3,4-dihydroxyphenyl)- alanine to dopamine happens during transfer.

An orally active CNS drug desires not only adequate metabolic stability to maintain integrity in the intestine and liver but also across the BBB. On the other hand, a drug can be pushed back into the blood by a dynamic transferal process, mostly through p-glycoprotein, using an ATP efflux tool.[13-15]

On a molecular level, the BBB is not homogenous but consists of a number of partially overlapping zones contained in a highly anisotropic lipid bilayer.16 The conformational mobility of the lipid chains is relatively low at or near the water (blood)/lipid interface and increases strongly toward the interface at the center of the bilayer. The lipid-water edge is linked with a layer of perturbed water molecules with considerably dissimilar polarization properties. Because of this, the capacity of these water molecules to form hydrogen bonds with drug particles is intensely reduced and forms share of the desolation procedure. In addition, the hydrophilic/lipophilic interface at the blood/membrane borderline comprises of perturbed and bound water, charged polar lipid head moieties linked to long lipid chains. As a result, a drug approaching the BBB is confronted with a thick layer that is capable of non-covalent interactions with the drug, likewise to that of receptor but with much looser steric necessities. The majority of drug BBB penetration is through passive diffusion through the cellular membrane. How this is accomplished has been the subject of significant research.

3. PRODRUG APPROACHES FOR IMPROVED BRAIN DRUG DELIVERY OF SMALL MOLECULES

An interesting medicinal chemistry-based strat¬egy to improve the brain uptake of small-mol¬ecule drugs is to create prodrugs that require biotransformation, either enzymatic or chemical, prior to their therapeutic activity.[17-18] Since lipophilicity is a factor favoring good BBB pen¬etration, most of the early prodrug examples focused on modifying a drug to make it more lipophilic by masking its polar and/or ionizable groups. This approach has been encouraged by the successful examples of methylated and diacetylated forms of morphine, codeine and heroin.[19] Since both prodrugs are more lipophilic than morphine, they cross the BBB quickly; approximately ten-times faster in the case of codeine and 100-times faster for heroin. Some of the other lipophilic CNS prodrugs having modest success are those that readily enter the brain and are rapidly converted within brain tissue to more hydrophilic, often charged, intermediates.[20-21] Depending on the rate of regeneration of active drug from the intermediate that has become trapped in the brain, it is possible to achieve sustained pharmacological activity.

4. HIGH-THROUGHPUT SCREENING (HTS)

High-throughput screening (HTS) is a technique for scientific investigation particularly used in drug discovery and related to the fields of biology and chemistry. HTS aims to rapidly assess the activity of a large number of compounds on a given target. Therefore, the identification and validation of target are the most critical steps for the success of HTS-based drug discovery. Through this procedure one can quickly recognize active compounds, antibodies, or genes that modulate a specific biomolecular path. The results of these experiments provide initial points for drug design and for considerate the contact or role of an exact biochemical procedure in biology.

Typically, approximately a million compounds are tested at a primary screening step, in a parallel fashion using 96-, 384-, or 1536-wells in a matter of days. Full- or semi-automation of liquid handling, sample preparation, running of the actual assays, and data analysis are necessary for efficient HTS. Unlike low-throughput assay, HTS development requires careful considerations of reagent stability (i.e. oxidation), cost, environmental control (such as, temperature, fluctuation and physical agitation) and many other potential artifacts. For example, some small molecules have their own fluorescent signals that can interfere with the fluorescent-based assay itself. In a cell-based assay, proteins in the cell culture media could bind to testing chemicals and prevent the action of compounds. Molecules with the high potential of covalent attachment to protein need to be excluded from screening. Many drug candidates are insoluble in water and require dimethyl sulfoxide (DMSO) or other solvents to dissolve initially. Less than 0.1% of DMSO is acceptable for screening and the plate to plate variability should be kept below 10% coefficient of variation (CV). Although the use of primary cells derived from animals or patients may be ideal, the huge quantity of cells required for drug screening limits the use of primary cells. Advance of induced pluripotent stem cells (iPS) technology might provide a solution to this problem. If an assay relies on a kit from commercial providers, it is strongly recommended to test multiple kits from different companies before investing time and effort on screening million compounds.[22]

5. DESIGNING SMALL MOLECULES WITH IMPROVED LATENT FOR CNS BIOAVAILABILITY

Effectiveness can be restricted if the drug is incapable to reach the target in satisfactory quantities during the suitable time window. The level of poor CNS bioavailability is signified by assessment that only 2% of drugs of small molecules and nearly no proteins and nucleic acid therapeutics enter the blood-brain barrier (BBB).[23] Bioavailability can meaningfully pay to drug safety and efficacy. Hence, creating effective drug concentration in the brain is a major task in the growth of CNS therapeutics. The biological procedures underlying the in vivo fate of a small molecule drug are knowingly inclined by the drug's physical characters, termed "molecular properties". Molecular properties represent the characters that support to create a chemical into a drug. Statistical analyses of molecular properties have been supportive in recognizing general trends connected with oral bioavailability (Table 1). However, CNS targeting drug discovery needs a more rigorous and diverse set of parameters and concerns due to BBB (Table 1).

Table 1. Molecular properties essential to be a good CNS drugs

Rules of 5 for oral drugs	**Modified rules for CNS drugs**
Less than 5 LogP (Lipophilicity)	Less than 4 LogP (Lipophilicity)
Less than 500 Daltons Molecular weight	Less than 400 Daltons Molecular weight
Less than 5 Hydrogen bond donors	60 - 100 Å2 Polar surface area
Less than 10 Hydrogen bond acceptors	

The major tools for delivery of substances into the CNS are trans-membrane diffusion and saturable transporter. Maximum CNS therapeutics are small, lipid soluble molecules that are expected to cross the BBB via trans-membrane diffusion. Although some biopharmaceuticals, such as peptides and even small proteins, have a measurable trans-membrane diffusion, saturable transporter are the maximum effective device for delivering these molecules into the CNS. A chemical with low molecular weight and high lipid solubility favors crossing by trans-membrane diffusion mechanism. Though, growing lipid solubility too much can also affect with BBB penetrance, since a drug that is too lipophilic can be sequested by the capillary bed and does not reach the cells behind BBB. The bioavailability of a drug in the brain is determined not only by the transport efficiency across the BBB but also by the amount of drug available to the brain. Peripheral tissues take up chemicals with higher lipophilicity, thus limiting the amount of the drugs in the blood stream. Additionally, increasing the lipophilicity of a molecule to increase transport can also result in making it a substrate for the efflux pump P-gp. Thus, high lipid solubility could lower the quantity of drug reaching to the BBB, although it will increase transport rate across the BBB. Taken together, increase of lipid solubility does not necessarily lead to better CNS bioavailability and its effect on decreased concentration in the blood should be taken into consideration.

Diminishing polar surface area (PSA) has been one more approach to increase BBB penetration but this methodology also needs a careful implementation. In general, PSA distinguishes CNS penetrating compounds better than the conventional lipophilicity (LogP). Growing logP and reducing PSA are used to advance brain uptake of small molecules, but these alterations could also increase

the probability that the small molecule will serve as a cytochrome P450 (CYP), especially CYP2D6, substrate. The CYP system in the liver is chiefly responsible for the first phase in the metabolism and elimination of several endogenous molecules and exogenous chemicals. Among the subtypes, cytochrome P450 2D6 (CYP2D6) is one of the most significant enzymes involved in the metabolism of drugs. CYP2D6-mediated undesirable metabolism of drug will bound brain uptake by dropping systemic drug bioavailability and pharmacodynamics. Hence, when the PSA and Log P values of drug applicants are revised to advance brain uptake, there is a potentially undesired consequence of producing suitable CYP2D6 substrates. Optimization of a compound to improve brain uptake must be done cautiously to minimize the likelihood of creating good CYP2D6 substrates.

6. TOXICITY TESTING

In addition to the absence of efficacy, toxicity of drug applicant is one of the main scientific motives for failure of drug discovery effort. Toxicity can be analyzed in the way of both acute and chronic patterns. Acute toxicity involves injurious effects on an organism over a single or short-term exposure for one or two week's period. Chronic toxicity is the capability of a compound to cause toxic effects over a prolonged period of time, generally by frequent or constant exposure that could last for the whole life of the exposed organism. Screening procedures include a P450 inhibition assay using either recombinant cytochrome P450 enzymes or liver microsome as well as MTT (3-(4,5-Dimethylthiazol-2-yl)-2,5 diphenyl tetrazolium bromide) or other equivalent one, such as MTS (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium))-based cytotoxicity assays. Toxicity consequences from these in vitro assays flag hits or lead compounds for further consideration which compounds can advances into the next preclinical studies.[24]

It is significant to plan the *in vivo* toxicity experiments while considering whether a particular animal species is the best option for disease sign of interest. The metabolic and toxicity profiles of chemical could be broadly different depending on which species were used. It is not simply expectable to bring the toxicity between species. Such possible inter-species sensitivity needs to be considering before proceed to the expensive next step of clinical trials. Since animal toxicology tests need comparatively large quantities of compound, practical issues with mass production of chemical should be well-thought-out in advance. The purity of the compound needs to be very high in order to ignore potential toxicities of impurities.

7. MISUNDERSTANDING REGARDING NATURAL PRODUCTS AND OFF-LABEL USE OF APPROVED DRUGS

Misapprehension of safety concerning "natural" product is a serious alarm, since many public undertakes that natural products are inherently safe. For instance, caffeine is a natural product and has been an ancient source of drugs for applicant compounds. It is also very safe. A fatal dose is more than 10 g, which would need drinking 80–100 cups of coffee in rapid succession. Thus accidental overdose is not an easy thing to do. Though, natural products are not inherently safer than engineered or synthetic products. For example, arsenic is a natural product but it is very noxious with acute nominal lethal dose of 70-200 mg. Misconception about off-label use of permitted medication is an even more serious problem. Drugs are approved by regulatory agencies for "a specific" disease symptom. Thus, the clinical use of an approved drug for another disease or ignoring dosing recommendations is not necessarily safe. In terms of drug development, beginning a new drug discovery with drugs already approved for another disease indication is not always inherently safer.

8. FUTURE TRENDS

By quick progress of genomics, proteomics, and metabolomics technologies, strategy for drug discovery and development will turn into more effective. Biomarkers and personalized medicine will remain to be the main interests in the upcoming drug development.

Biomarkers are characteristics that are demonstrably measured and assessed as indicators of basic pathogenic procedures, or pharmacologic replies of patients to therapeutic intervention. For example, high-density lipoprotein and low-density lipoprotein cholesterols are well-established biomarkers of cardiovascular maladies. Biomarkers can be used to recognize patients at higher risk, differentially diagnose a disease, evaluate the severity and advancement of disease, predict prognosis, and serve as surrogate marker of safety and efficacy. In drug development, biomarkers also support to identify and stratify patients who are most likely to reply well to a particular treatment or are least likely to suffer side-effects. Discovery of new biomarkers for determining activity and toxicity of drug at an early stage will meaningfully develop the clinical trial study design and decrease attrition rates. Given the potential of biomarkers in the individualized treatment, biomarkers are gaining momentum in the personalized medicine field. For CNS disorders, biomarkers have additional important use. Due to the relative inaccessibility of CNS, earlier detection of underlying pathogenic process in the brain has been one of the major obstacles in drug development for CNS disorders. Recognition of ongoing disease methods during clinically silent period may deliver a better treatment frame and a customized therapeutic intervention based on disease heterogeneity. Since the rate-limiting factors for most biomarker

discovery are the quality and depth of the clinical data and samples, strong teamwork between pharmaceutical industry and academic institution is essential for biomarker development.

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