JPP Journal of Pharmacy and Pharmacology
ROYAL PHARMACEUTICAL SOCIETY

JPP Journal of Pharmacy and Pharmacology

JPP 2011, 63: 136–139

Received September 18, 2009
Accepted June 17, 2010
DOI
10.1111/j.2042-7158.2010.01161.x
ISSN 0022-3573

Short Communication

Exploring neurotherapeutic space: how many neurological drugs exist (or could exist)?

Donald F. Weaver[a,b] and Colin A. Weaver[b]

[a]Department of Medicine (Neurology), [b]School of Biomedical Engineering, Dalhousie University, Halifax, Nova Scotia, Canada

Abstract

Objectives Since high-throughput screening of compound libraries (virtual or real) against druggable targets is increasingly being used to discover therapies for brain disorders, it is crucial to ascertain if such screening methods adequately explore 'neurotherapeutic space (i.e. the total number of molecules that are or could be neuroactive)'. We present an approach to providing an estimate of the size of neurotherapeutic space.
Methods Molecular modelling and statistical calculations were used to determine the number of molecules, which exist or could exist, with the necessary physicochemical and structural properties to be neurologically active drugs.
Key findings Assuming eight fundamental types of drug–receptor interactions, five different functional groups per type of interaction and five different molecular platforms for each functional group array, we calculated the total number of molecules that could be contained within a 7 Å radius sphere, used to define neuroactive chemical space. This calculation revealed that there are 6×10^{15} molecules that could be neurological drugs.
Conclusions Clearly, when it comes to exploring neurochemical space, we are still in our infancy and conventional high-throughput screening provides only a very limited sampling of the neuroactive chemical space that is available to neurotherapeutic compounds.
Keywords bioinformatics; cheminformatics; neurological drugs; molecular modelling

Introduction

One of the fundamental goals of modern neuropharmacology research is to identify new 'druggable' receptors within brain. These druggable receptors are isolated and characterized with the expectation that they can be used to screen libraries of chemical compounds to discover new, neurological therapeutics.[1] Such expectations are in keeping with current approaches to drug discovery based upon high-throughput screening methods.[2,3] However, can standard screening methods using conventional compound libraries truly explore 'neurotherapeutic space' in a manner that meaningfully captures the structural diversity of neuroactive drugs? Moreover, what allows a molecule to behave as a neurological drug, and is it possible to estimate the total number of molecules that exist (or could exist) with the required properties to be neurological drugs? The need to answer these questions is a priority in neuroscience because of the ever-expanding use of bioinformatics to tackle the burgeoning need for new brain therapeutics. We herein present an approach to providing a *conservative* estimate of the size of neurotherapeutic space, and use this approach to determine the number of molecules with the necessary physical properties to be 'small molecule' neurologically active drugs. No estimate of the size of neurotherapeutic space has been previously presented.

Methods

Calculations to determine the optimal conformations and geometries of drug molecules were performed using molecular mechanics force field calculations.[4] All molecular modelling calculations were carried out in the Molecular Operating Environment (MOE), version 2005.6 (Chemical Computing Group, Montreal, Canada).[5] Structures were geometrically optimized using energy minimization calculations with the MMFF94x force field (and partial charges as implemented in the MOE program) with the convergence limit set to 0.05 kcal/mol/Å. A bond rotation-based conformational search was performed for each

Correspondence: Donald F. Weaver, Departments of Medicine (Neurology) and Biomedical Engineering, Dalhousie University, Halifax, Nova Scotia, Canada B3H 4J3.
E-mail: donald.weaver@dal.ca

compound to enable a grid search of the molecular potential energy surface. Calculations to determine the number of molecules in neurotherapeutic space were completed using the Maple 10 Mathematics and Engineering Software suite, employing standard probability equations to comprehensively count the number of all possible connections for each grouping of molecules, and then summing these numbers.[6]

Results and Discussion

Providing a conservative estimate of the total number of molecules that could be neurological drugs requires multiple assumptions. It is necessary to determine what makes a molecule behave like a drug, then to ascertain what makes a drug behave like a neurological drug, and finally to determine how many such molecules exist.

All drugs are molecules, but all molecules are not drugs. A drug molecule possesses one or more functional groups positioned on a structural framework that holds the functional groups in a defined geometrical array that enables the molecule to bind specifically to a targeted receptor. The structure of the drug molecule thus permits a desired biological response, which should inhibit pathological processes and which should preclude binding to other untargeted receptors (thereby minimizing toxicity). The framework upon which the functional groups are displayed is frequently chemically inert so that it is metabolically stable. The structural framework should also be relatively rigid to ensure that the array of functional groups is not flexible in its geometry, thus preventing the drug from interacting with untargeted receptors by altering its molecular shape. To be successful in countering neuropathology, however, a drug molecule must have additional properties beyond the capacity to bind to a defined receptor site. It must be able to withstand the journey from its point of administration until it finally reaches the receptor site within brain.[7]

Therefore, a drug, whether neuroactive or not, is a defined piece of molecular architecture possessing the capacity to retain structural integrity and to establish unique energetically favourable intermolecular interactions with complementary contact points on a desired receptor macromolecule; these intermolecular interactions are mediated via clusters of atoms (i.e. functional groups) positioned in a fixed three-dimensional arrangement on a central molecular platform.[7] Eight fundamental intermolecular interactions primarily contribute to the drug–receptor docking process: anionic or cationic electrostatic interactions; positively or negatively charged dipole interactions; hydrogen bond donor or acceptor interactions; aromatic–aromatic (stacking) or non-aromatic lipophilic interactions.[7] As a conservative estimate, approximately five different functional groups (frequently more) can contribute to each one of these intermolecular interactions; for example, an anionic carboxylate group may also be bioisosterically represented by a sulfate, sulfonate, phosphonate or tetrazole (where bioisosteric means structurally distinct but biofunctionally equivalent). Similarly, as a conservative estimate, the central molecular platform that holds the functional group array in three-dimensional space may also be represented by 5–10 (frequently more) different platforms per geometrical disposition; for instance, naphthalene, anthracene, phenanthrene, quinoline and isoquinoline can all display two functional groups at a fixed separation of 6.7 Å. These structural properties required for a molecule to possess drug-like properties have been effectively summarized by Lipinski's rules.[8–10]

To be neuroactive, however, a molecule must be more than just drug-like; it must also first cross the blood–brain barrier [BBB] so that it can actually enter the central nervous system. The BBB is an anatomical/physiological mechanism that influences the permeability of brain capillaries, such that most compounds are prevented from entering brain tissue. The BBB is physically constituted by the brain's capillaries, which are unique in two ways: firstly, the endothelial cells that constitute these vessels are joined by tight junctions that prevent water-soluble substances from freely entering the brain; secondly, these capillaries are enclosed by the 'end-feet' of astrocytic cells that also act as a barrier. Drug molecules may cross the BBB by either passive diffusion or active transport, with the former being preferred because of its capacity to accommodate greater molecular diversity.

The two primary molecular properties that dictate BBB permeation by passive diffusion are size (molecular weight (MW) <450 g/mol) and solubility (optimal lipophilicity, as determined by an octanol-water partition coefficient (logP) value of 1.5–4.0).[11–13] Then, once the drug passively diffuses across the BBB, its three-dimensional functional group array (pharmacophore) selectively binds to a receptor to elicit a selective neuropharmacological response. To achieve selectivity, the drug's pharmacophore establishes interactions with the receptor via specific intermolecular interactions at multiple points of contact.

To ascertain the size of neuroactive chemical space it is necessary to translate these diverse physicochemical requirements into manageable molecular properties. First we addressed the molecular size criterion. We used molecular mechanics energy minimization calculations to optimize the geometries of 200 neuroactive drugs and drug-like molecules with MW < 450 g/mol; these structurally diverse drug molecules included anticonvulsants, antipsychotics, antidepressants and other agents used in the treatment of movement disorders and dementia (Alzheimer's disease). A list of the compounds used to define the size of neurotherapeutic space is given in Table 1. These calculations showed that any of these 200 drug molecules could fit into a 7 Å radius sphere – suggesting that neuroactive space can be represented by a 7 Å radius sphere. Next we addressed the solubility and selectivity criteria. A molecule with too many functional groups will have solubility (and size) problems: a molecule with too many polar groups (e.g. ionic groups) will have a negative logP (and will be too water soluble to cross the BBB); a molecule with too many apolar groups (e.g. alkyl/aryl groups) will have too large a logP (and will be too lipid soluble to be absorbed and distributed to the brain). Thus, we concluded that to be neuroactive a molecule should fit within a 7 Å radius sphere (size criterion), have an adequate balance of polar/apolar functional groups (solubility) and have five or less (but more than one) interaction points of contact with the receptor (selectivity, size and solubility).

Assuming eight types of intermolecular interaction, five different functional groups per type of interaction and five

Table 1 List of neuroactive agents used in defining size of neurotherapeutic space

Anticonvulsant agents	Tricyclic antidepressants
Barbiturates	Amitriptyline
Phenobarbital	Doxepin
Primidone	**Movement disorder agents**
Benzodiazepines	Anticholinergic Drugs
Clobazam	Benztropine
Clonazepam	Biperiden
Carboxylic Acids	Ethopropazine
Valproic Acid	Procyclidine
GABA Derivatives	Trihexyphenidyl
Vigabatrin	COMT inhibitors
Gabapentin	Entacapone
Pregabalin	Dopaminergic agents
Hydantoins	Dopamine agonists
Phenytoin	Bromocriptine
Iminostilbenes	Pergolide
Carbamazepine	Pramipexole
Oxcarbazepine	Ropinirole
Succinimides	Dopamine precursors
Ethosuximide	Levodopa
Methsuximide	Monoamine oxidase inhibitors
Other sodium channel antagonists	Selegiline
Lamotrigine	**Psychoses**
Topiramate	Benzisoxazoles
Anxiety disorders	Risperidone
Azaspirodecanediones	Butyrophenones
Buspirone	Haloperidol
Benzodiazepines	Dibenzodiazepines
Alprazolam	Clozapine
Lorazepam	Dibenzothiazepines
Attention deficit disorder	Quetiapine
Stimulants	Dibenzoxepines
Dexamphetamine	Loxapine
Methylphenidate	Diphenylbutylpiperidines
Dementia drugs	Pimozide
Cholinesterase Inhibitors	Phenothiazines, aliphatic
Donepezil	Chlorpromazine
Galantamine	Methotrimeprazine
Rivastigmine	Phenothiazines, piperazine
Depression	Fluphenazine
MAO Inhibitors	Perphenazine
Phenelzine	Phenothiazines, piperidine
Tranylcypromine	Pericyazine
Selective serotonin reuptake inhibitors	Thioridazine
Citalopram	Thienobenzodiazepines
Fluoxetine	Olanzopine
Serotonin-norepinephrine reuptake inhibitors	Thioxanthenes
Venlafaxine	Flupenthixol
	Thiothixene

Note: 200 compounds were used to determine the size of neurotherapeutic space. For brevity all are not listed in this table. For example, 20 benzodiazepine and 20 phenothiazine analogues were used. Analogues of phenytoin (5-ethyl-5-phenylhydantoin) were also used.

different molecular platforms for each functional group array, we calculated the total number of two-, three-, four- and five-points of contact molecules that could be contained within a 7 Å radius sphere, assuming a minimal functional group separation of 1.6 Å (approximate length of a C-C bond)

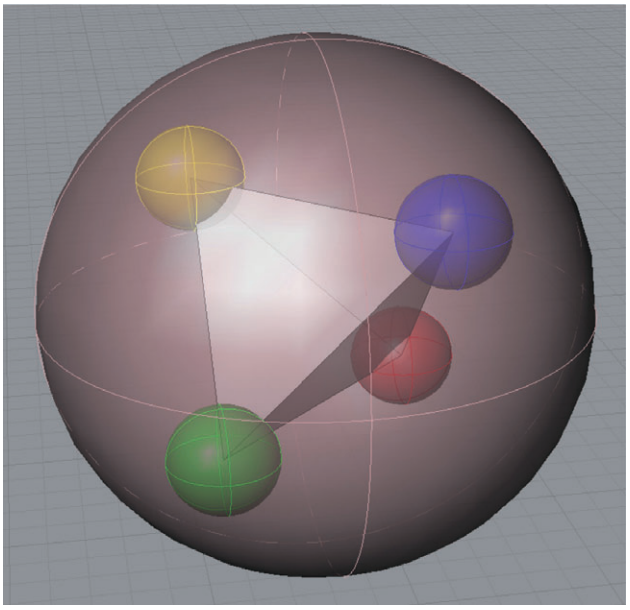

Figure 1 Neuroactive chemical space represented as a 7 Å radius sphere. A representative 4-point of contact molecule with four functional groups appended to a central molecular platform is one of 10^{15} neuroactive drug-like molecules existing in this space.

(Figure 1). To estimate the size of this neurotherapeutic space we initially ascertained the number of possible functional group volume units that could occupy a 14 Å sphere. This was calculated by assuming a 'minimal functional group volume' size as a 1.6 Å sided cube (i.e. constituting a 'volume pixel'). We then ascertained 350 distinct packing points for these functional group volume units within the sphere. Knowing that there are 350 volume units in the sphere and that at each unit 40 types of functional group could exist (eight interaction types times five functional groups) on five platforms, we calculated the number of possible permutations (nPr = n!/r!(n-r)!) of molecules for each of 2-, 3-, 4- and 5-point possibilities. For example, the number of possibilities for a two functional group molecule was found to be 2 656 725. These steps were repeated for the 3-, 4- and 5-point molecules. From this number was subtracted the subset of molecules that had multiple polar functional groups, such that their logP was too low, or conversely had too many apolar functional groups, such that their logP was too high. The final sum revealed that there exist 6×10^{15} molecules that could in principle be neurological drugs.

As previously discussed, drug-like molecules may also cross the BBB by routes other than passive diffusion, including active transport or transcytosis. However, such compounds have not been included in the overall total since they add only 10^{7-8} molecules – a numerically insignificant contribution.

It must be emphasized that the value 6×10^{15} is a conservative estimate for the size of neurotherapeutic space. For example, if we assume seven platforms for each potential drug, rather than five, then the size of neurotherapeutic space rapidly expands to 3.6×10^{16}, and to 1.3×10^{17} for nine platforms (and the assumption of seven, or nine, rather than five

platforms is still a relatively cautious and reasonable extension). However, the goal of this study was to ascertain a conservative estimate of the size of neurotherapeutic space. In these calculations, we have assumed five possible bioisosteres for each functional group and five central platforms for each putative drug. For most functional groups and most central platforms, it is possible to identify 10–12 equivalent bioisosteres or alternative platforms, which would increase the size of neurotherapeutic space to 10^{21} molecules. We have selected five of possible bioisosteres and platforms to ensure the likelihood of synthetic accessibility, rather than having simply 'theoretically possible' molecules.

Conclusions

Based upon the assumptions employed in this study, a conservative estimate suggests that there exist 6×10^{15} small molecule neuroactive therapeutics. Although estimates vary, in theory there are approximately 10^{200} possible different 'small' organic molecules in the universe; of these, 'only' about 10^{60} have drug-like characteristics.[14–17] The assumptions employed by us to determine the size of neurotherapeutic space are different from these other studies; these other studies have determined the size of 'therapeutic space', making direct comparisons difficult. However because of the BBB, not all drugs are neuroactive drugs, and thus a subset of 10^{15} of these 10^{60} drug-like molecules have what it takes to be neuroactive. The Beilstein database, which covers chemistry from 1779 to the present, contains only 10^{7} known molecules.[1,14] Clearly, when it comes to exploring neuroactive chemical space, we are still in our infancy and conventional high-throughput screening provides only a very limited sampling of the neuroactive chemical space that is available to neurotherapeutic molecules.

Declarations

Conflict of interest

The Author(s) declare(s) that they have no conflicts of interest to disclose.

Funding

This work was supported by the Canadian Institutes of Health Research.

Acknowledgements

This work was supported in part by funding from the Canadian Institutes of Health Research. DFW acknowledges salary support from a Canada Research Chair, Tier 1, in Neuroscience.

References

1. Gorse AD. Diversity in medicinal chemistry space. *Curr Top Med Chem* 2006; 6: 3–18.
2. Bleicher KH *et al*. I Hit and lead generation beyond high-throughput screening. *Nat Rev Drug Discovery* 2003; 2: 369–378.
3. Gasteiger J *et al*. Neural networks as data mining tools in drug design. *J Phys Org Chem* 2003; 16: 232–245.
4. Allinger NL *et al*. Molecular mechanics. *J Amer Chem Soc* 1989; 111: 8551–8556.
5. *MOE*. Montreal, Quebec, Canada: Chemical Computing Group Inc., 2005: 06.
6. Maple 10 Mathematics and Engineering Software Maplesoft A Division of Waterloo Maple Inc University of Waterloo, 2007.
7. Nogrady T, Weaver DF. *Medicinal Chemistry: A Molecular and Biochemical Approach*, 3rd edn. New York: Oxford University Press, 2005: 9–24.
8. Lipinski CA. Drug-like properties and the causes of poor solubility and poor permeability. *J Pharmacol Toxicol Methods* 2000; 44: 235–249.
9. Lipinski CA *et al*. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 1997; 23: 3–25.
10. Lipinski CA *et al*. Experimental and computational approaches to estimate solubility and permeability in drug discovery and development settings. *Adv Drug Deliv Rev* 2001; 46: 3–26.
11. Clark DE. In silico prediction of blood-brain barrier permeation. *Drug Discov Today* 2003; 15: 927–933.
12. Crippen GM, Wildman SA. Prediction of physicochemical parameters by atomic contributions. *J Chem Inf Comput Sci* 1999; 39: 868–873.
13. Goodwin JT, Clark DE. In silico predictions of blood-brain barrier penetration considerations to 'keep in mind'. *J Pharmacol Exp Ther* 2005; 315: 477–483.
14. Bohacek RS, McMartin C. Exploring the universe of molecules for new drugs. *Nat Med* 1995; 1: 177–178.
15. Bohacek RS *et al*. The art and practice of structure-based drug design a molecular modelling approach. *Med Res Rev* 1996; 16: 3–50.
16. Fink T, Reymond JL. Virtual exploration of the chemical universe up to 11 atoms of C, N, O, F: assembly of 26.4 million structures 110.9 million stereoisomers and analysis for new ring systems stereochemistry physicochemical properties compound classes and drug discovery. *J Chem Inf Model* 2007; 47: 342–353.
17. National Center for Biotechnology Information. The PubChem Project. http://pubchem.ncbi.nlm.nih.gov/ Accessed 1 September 2009.