Old Receptor Space Essay

The cloning and development of binding assays for large numbers of receptors opens a new "post genome" era of pharmacology. It is now possible to invert the traditional approach to pharmacological selectivity: to find a drug that is selective at one receptor, and then observe its behavioral effects. A complementary approach is to find a drug that is behavior selective, and then observe its receptor binding profile. The psychedelics are a family of drugs whose qualitative diversity has not been fully acknowledged by the field of molecular pharmacology. This work is focused on understanding the mechanisms underlying the qualitative diversity of psychedelics, and using that knowledge to contribute to an understanding of the chemical organization of the human brain and the mind that emerges from it.

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Introduction

Why are there so many different neurotransmitter receptors in the brain? What is the functional role of each, and how are they organized in the brain? How are the activities of these transmitter systems and their interactions associated with mental states? In short, what is the chemical architecture of the brain and the mind that emerges from it?

The pharmacological approach to these questions is to develop compounds that bind selectively at receptors, and activate or block them, and use them as probes to receptor function. When the molecular mechanisms of action of a drug are known, they can be correlated with the behavioral effects in animals or the subjective reports of humans, to understand the mental correlates of their underlying biological effects. When used in this way, pharmacology is a means of exploring the chemical organization of the brain and mind.

Receptor Space

Traditionally, pharmacologists have searched for drugs that are selective for single receptors, so that they can manipulate those receptors independent of others, to determine their function. However, to be useful or interesting, a drug does not have to be selective for just one type of receptor. Theoretically, we want to know not only the role of individual receptors, but also their interactions. Often, the key to efficacy in treating mental disorders is not selectivity for a single receptor, but rather the right combination of activities at several receptors. The observation that our most effective current treatments for schizophrenia (atypical antipsychotics) bind at multiple receptors suggests that multiple receptor systems may be involved in the etiology of the disease. Thus to understand the nature of the illnesses we must not limit ourselves to one-by-one manipulations of receptor systems.

In order to discuss selectivity, consider a metaphor, or image, of a coordinate system based on receptors, one axis for each receptor (the "receptor-space"). From a pharmacological point of view, the origin of the receptor space represents the state of an individual brain at any moment, without the application of any drug. When a drug is applied that binds to receptors, it shifts the balance of activity of the brain away from the origin, by a vector representing displacement along the axes corresponding to the receptors where the drug binds (and perhaps others due to secondary interactions).

The distance of the shift could be thought of as occurring up to a maximum of full activation in which case the axis has a range from zero to one. Negative axes could correspond to blocking or deactivation of the receptor. Drugs which are absolutely selective for one type of receptor would have a non-zero value on only one axis. We can refer to these as "on-axis", and molecules with a non-zero value on more than one axis as "off-axis".

Selectivity has been a holy grail of pharmacology. Originally, it was selectivity that revealed the existence of receptor sub-classes. Beyond this historic role, in theory, if we have a drug that binds exclusively at one class of receptor, it allows us to manipulate that receptor independently of all the others, and provides the best opportunity to understand the functional and organizational role of that receptor.

If most pharmacologists could design their ideal research molecules, each one would have a high value on one axis and a zero value on every other axis (on-axis), and there would be an agonist (activate), an antagonist (block), and an inverse agonist (deactivate) for each axis. While this pharmacologists' research set is an especially important on-axis basis set, it can also be valuable to work with additional compounds that scatter widely and evenly through the off-axis space, effectively sampling the entire space at some resolution. The goal would be to populate receptor-space with chemical probes that allow us to learn the mental correlates of shifting a brain into any and all regions of the space.

In pharmacology, "selective" is a relative term. SSRIs are by definition selective inhibitors of the serotonin transporter. However, further studies have shown that some of them have high affinities at other receptors. Our concept of selective depends on how widely we have looked. Can we say that anything is selective until it has been screened against the entire receptorome? Are even "selective" drugs actually on-axis? Are any drugs absolutely on-axis? If two drugs each bind to a dozen receptors, with no overlap, then neither of them is selective in a conventional absolute sense, but they are selective relative to one another.

Clinically, there was an early focus on selectivity to remove the side effects resulting from unwanted receptor bindings, such as in tri-cyclic antidepressants, leading to the highly selective SSRIs. More recently, the trend has been to add multiple bindings to improve tolerability and efficacy, especially for resistant patients. Antipsychotic evolution has followed a similar pattern, starting with the unselective phenothiazines with unwanted side effects. Moving then to pure D2 blockers to remove unwanted side effects. Subsequently the SDA drugs were developed adding serotonin actions to dopamine, to get the right mix of properties, to treat additional symptoms

and to help refractory patients. Some of the most effective drugs, such as clozapine, have the widest binding profiles. It has come to be seen that selectivity in itself is not the solution, but rather what is effective is the right profile of multiple bindings.

Thus in clinical psychopharmacology, on-axis drugs are generally less effective than off-axis drugs. We need at least a retreat from an emphasis on absolute on-axis selectivity, and ideally a serious and systematic exploration of all regions of receptor-space. We should not limit our exploration to on-axis receptor-space (which mathematically speaking, is an infinitely small portion of the entire space). We need to understand what mental states are associated with various regions of the receptor-space. We need to understand what kinds of interactions between transmitter systems and neural pathways result from chemical perturbations into various regions of receptors space.

This knowledge can help us to build a theoretical foundation for the rational design of off-axis drugs for the treatment of mental illness. In a loose sense, mental illnesses are also a kind of perturbation in receptor-space, and it appears that these are off-axis perturbations. We need to determine what regions of receptor-space are associated with these illnesses, and develop a pharmacology for these off-axis regions.

Psychedelics

One approach to this problem involves a deeper study of a family of compounds, the phenethylamines, tryptamines, and ergolines, whose diversity of actions seem not to have been acknowledged in the molecular pharmacology literature. These compounds may provide an unexpectedly rich set of probes of receptor systems. The value of psychedelics lies in their diversity of qualitative effects and pharmacological profiles, combined with the fact that they provide a direct and immediate read-out of mental state. The provoked mental state can then be correlated with the pharmacological effects of the drug to reveal the chemical architecture of the mind.

Much work with "hallucinogens" has focused on finding the single receptor that is common to all hallucinogens, as the key to understanding their mechanism of action. It is time to address the complementary question: what is the mechanism underlying their qualitative diversity of actions, and what does it teach us about the chemical architecture of the human brain/mind?

The term "hallucinogen," favored by prominent pharmacologists, may reflect the search for the common mechanism of action of the "classic hallucinogens," and therefore a need to homogenize them. When we choose to explore the diversity of effects of the psychedelics, we recognize that hallucination is only a single entry on the list of effects. It seems that most of the names applied to this family of compounds carry one kind of value judgment or another: psychotomimetic, empathogen, etc. The option that will be used here is "psychedelic."

DIPT causes auditory distortion. 5-MeO-DIPT enhances orgasm in males but not females. MDMA provokes empathy. TMA provokes anger. Mescaline provokes an appreciation of beauty. 2C-B causes tactile, gustatory and sexual enhancement. 2C-E provokes rich fantasy and

introspection. The interesting issue is not so much that small molecular changes cause large changes in subjective effects, but that taken collectively, these compounds provide a rich set of tools for probing and revealing the chemical architecture of the brain/mind. How is it possible that chemical probes can selectively produce such diverse mental phenomena? This data is telling us something about the chemical organization of the human brain and the mind that emerges from it; something we can never learn from animal or molecular studies alone.

There may not be any other pharmacological family that generates as rich a diversity of mental effects. It is plausible that diverse spectra of receptor selectivity underlie the subjective diversity. Glennon is beginning to dissect the psychedelic experience into three components: an amphetamine effect, a DOM effect, and a PMMA effect. Nichols has suggested that visual effects may be due to activity at the 5-HT_{1A} receptor rather than the 5-HT_2 receptors. It is likely that additional components of the psychedelic experience can be decomposed and understood in terms of interactions with specific receptors or receptor combinations. It is surprising that the molecular pharmacology community has not more directly addressed the diversity of this set of tools.

The reticence of the research community to address this question might in part be due to their reluctance to acknowledge the validity of the human pharmacological data, as they may feel that much of it was not gathered with sufficiently "scientific" protocols, under strict clinical conditions with controls. Yet human data is rare and precious, such that we should not ignore the substantial body of data that exists. Will we always restrict ourselves to studying the head twitch, ear scratch, and lever choice of rodents while ignoring the richness of human experience reported in the existing data? Is it only a concern with the protocols used in collecting the data, or is there also a subtle social pressure, or fear of being labeled a drug advocate or mushy scientist if we acknowledge the human data and speak of empathy and fantasy rather than twitches and scratches?

The existing body of data seems to be quite compelling. It appears that every compound has unique subjective effects, although it would generally be difficult to clearly state what sets each one apart. Still, the literature suggests that there are a substantial number with clearly distinctive profiles, such as those cited above. Ignoring this data has caused the molecular pharmacology community to miss a potentially powerful set of tools, and to fail to ask some important questions about this family of compounds. It is time to take the bull by the horns and study what likely has attracted many of us to the field of neurobiology: the human mind.

Reading the human pharmacology of psychedelics suggests they may be widely scattered through the space of amine receptors. Not to suggest that they fill the entire space, only that they appear to be widely scattered in some parts of the space. A project funded by NIMH, "Multi-receptor structure-activity relationships of hallucinogens" has set out to document their distribution in this space.

The project has assayed twenty-two "amines" and three controls, each against more than fifty receptors, transporters and ion channels. These assays were conducted by the NIMH

Psychoactive Drug Screening Program. This preliminary survey is identifying the complete set of receptors that interact with psychedelics.

The motivation to conduct this study is based on accepting the human pharmacological data at face value. However, the study itself does not rely on the validity of the human data. The study will document the distribution of the psychedelics in receptor-space. If they have a wide distribution it should go a long way to explaining the diversity of effects. If they have a narrow distribution, then we need to look for another explanation, such as differential coupling of G-proteins.

The ultimate utility of this information would derive in part from connecting the receptor data to the subjective effects in humans. We can leverage the existing human data by including those compounds with human data suggesting distinctive profiles. By generating broad receptor activity profiles for an array of psychedelics with distinctive subjective effects, we are likely to generate many new hypotheses about how to dissect the different components of the psychedelic experience. It may then be possible to generate new animal models for some of these components to allow more intensive studies.

While we can leverage pre-existing human data, we can also select the set of compounds to assay with the objective of blanketing receptor-space as much as possible, and without limiting the study to materials for which human data exists. If the work demonstrates that the psychedelics sample a substantial region of receptor-space, then it may be possible to follow with clinical studies to complete the picture.

This project is not applied, it is academic. However, its aim is to lead to an understanding of the chemical organization of the brain and the mind that emerges from it. This understanding should ultimately provide a firmer basis for understanding mental illness and developing treatments.

Receptor Space Revisited

"Receptor space" has been discussed in the reference frame of the unmedicated brain. Drugs perturb the system from its pharmacological origin by altering the activity of transmitter and receptor systems, through increasing or decreasing transmission or transmitter levels, or up or down regulating receptor populations, etc. However, these kinds of changes occur spontaneously and constantly in the unmedicated brain. Thus our pharmacological reference frame, of the unmedicated brain at the origin, is a very dynamic one. There are other reference frames, which are useful to think about.

Let's consider a brain-centered reference frame, in which the origin is based on some arbitrary absolute levels of activity at each receptor population. The origin could be the time-averaged activity at each receptor, or no activity at each receptor, it doesn't matter much. In this reference frame, the state of the brain is constantly on the move, regardless of medication. We can think of it as a complex dynamical system, in which the trajectory likely does not traverse the entire receptor-space, but rather follows certain high-dimensional orbits, and switches among many "attractors," where the attractors represent the major emotional states and moods, and whatever

other mental phenomena the chemical systems are mediating. Mental illnesses can be thought of as pathological attractors.

In this more dynamic reference frame, the notion of drugs perturbing the brain along a vector of binding affinities in receptor-space seems simplistic. It is more likely that drugs will create a perturbation along the binding vector, thereby pushing the system into a new attractor.

As pharmacologists, we want to understand how patterns of activity at receptor populations associate with mental phenomena. We want to get to know the pharmacology of the attractors. It seems unlikely that the attractors will be on-axis, resulting from changes in the activity of single receptor populations.

We have our hands on the receptors and we are enchanted by them. We have come to think of selectivity in terms of receptors, and in the process we have lost sight of the mind that we wish to understand. There are other approaches to thinking about pharmacological selectivity. Selectivity can be defined in terms of different or distinct behavioral or subjective mental effects produced by drugs.

The conventional approach to pharmacology is to find a drug that is receptor selective, and then observe its behavioral effect. An alternative approach is to find a drug that produces a distinctive behavior, and then observe its receptor binding profile. This alternative approach may hold the greatest promise for understanding the pharmacology of the attractors, and thus the major mental states mediated by receptors. The two approaches are complementary, and we need both to provide the most comprehensive understanding.