

What Will Be the Psychotropic Drugs of Tomorrow?

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Abstract

The development of psychotropic has slowed over the last two decades for essentially economic reasons; the drug industry has invested more in the field of oncology and autoimmune diseases. However, there are still avenues to explore, such as allosteric for the development of drugs in the field of anxiety depression, bipolarity in particular. Other concepts are suggested in this article as the β -arrestins potential therapeutic targets in Alzheimer's disease (AD), the inhibitors of phosphodiesterase 10A for Huntington's disease, and the epigenetic in schizophrenia, peroxisome proliferator-activated receptors in neurodegenerative diseases.

Keywords

Psychotropic development; Allosteric; β -arrestins; Phosphodiesterase 10A; Epigenetic; Peroxisome proliferator activated receptors

Introduction

The development of psychotropic drugs, like that of other classes of drugs, has come to a halt in the past ten years for several reasons that are often not known to psychiatrists or neurologists.

The first reason that is not essential is the length and cost of development. The length is related to the fact that for several decades the regulatory requirements for safety have increased. On the other hand, it is increasingly difficult to find naive patients in rich countries and the corollary is that psychiatrists in these countries no longer participate in clinical research as part of a development for financial reasons or time constraint. Patients in rich countries are also reluctant to participate in such studies. Germany for historical reasons hardly accepts studies against placebo, as in Japan this type of study is not legal. Clinical trials are therefore mainly in Eastern Europe or in some developing countries. In the United States, the problem is that due to economic constraints the included patients are often study professionals.

Another most important factor is the fact that the leaders of the pharmaceutical industry who decide are not scientists or health professionals for the most part, have been fascinated by the progress of genetics and genomics. This resulted in abandoning all or part of classical psychopharmacology and abandoning conventional research and development programs. A decision reinforced by the drug agencies who criticized the pharmaceutical companies to create only "me-too".

To overcome these difficulties, firms have lowered the methodological requirements both in preclinical and clinical studies, leading to industrial disasters since Botched studies cannot lead to drug registrations [1].

Allosteric can play a role in the design of new psychotropic drugs

The concept of allosteric was proposed in the 1960s and the original model presented by Monod et al.[2] is still valid even though other models have been proposed. The concept translates the ability of a so-called allosteric ligand to regulate the activity of a biologically active protein by binding to a specific site different from the active or primary site. These two sites are structurally distinct but interactive: the binding of the allosteric ligand leads to an "allosteric transition", i.e. a reversible change in the conformation of the protein, leading to a modification of the biochemical characteristics of the binding of the primary ligand and also functional properties of the protein [3].

In other words, the allosteric proteins can exist spontaneously in at least two interconvertible conformational states (many allosteric proteins exist in multiple conformations in equilibrium), corresponding to different functional activities. Binding of a ligand stabilizes a particular conformational state of the protein and since this particular state corresponds to a given activity of the protein or inactivity; the allosteric ligands then exert a functional regulatory effect.

Article Information

DOI: 10.31021/jnn.20181116
Article Type: Research Article
Journal Type: Open Access
Volume: 1 **Issue:** 4
Manuscript ID: JNN-1-116
Publisher: Boffin Access Limited

Received Date: 05 July 2018
Accepted Date: 01 August 2018
Published Date: 08 August 2018

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Citation: Bourin M. What Will Be the Psychotropic Drugs of Tomorrow? J Neurosci Neurosurg. 2018 Aug;1(4):116

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The answer is positive and several examples are a striking demonstration of the application of this mechanism to the drug; it also appears that the future development of such therapeutic tools represents a formidable possibility of pharmacological novelties.

The advantages of such drugs over conventional agonists or antagonists are many. On the one hand, the binding interactions between the allosteric ligands are such that, schematically, everything happens as if only the excessively stimulated receptors were blocked by the allosteric regulator while the inactivated receptors remain unchanged; this avoids a large part of the adverse effects of conventional drugs which affect without any distinction all the target receptors and either continuously stimulate the receptor or block it chronically, eventually causing reactions that modify the gene expression of these receptors. On the other hand, the recognition specificity of allosteric modulators is generally high, facilitating a narrower selectivity and in any case different from that existing for conventional drugs; once again, this property makes it possible to reduce the expected adverse effects of these allosteric agents by reducing the number of irrelevant targets reached by these drugs.

Existing examples of these allosteric regulators developed as therapeutic tools are, for some, already old but limited in number. At the level of neurotransmitter receptors or hormones, the best-known examples, involving the channel receptors occupy a place of choice. The cholinergic nicotinic receptor, in particular, has been and still is the reference prototype for fundamental studies; the presence of multiple allosteric sites (sites for local anesthetics, Ca^{2+} , ATP, substance P, physostigmine, steroids, cholesterol and other compounds) has been described.

GABA A receptors is the most striking example of the successful application of allosterism to drugs [4]. Indeed, these receptor channels are the target of various allosteric regulators of which at least two are of extreme importance: benzodiazepines on the one hand, and barbiturates on the other hand. Everyone knows the therapeutic revolution triggered by these products; Benzodiazepines, in particular, have been able to demonstrate in a most brilliant way the efficacy of allosteric regulators. However, the negative aspects of the use of these molecules (tolerance, dependence, and reduction of cognitive functions) have highlighted the importance of the definition of the targeted target. Current molecular biology studies differentiate GABA receptor subtypes according to their protein subunit composition and study their respective functional roles; they are likely to develop anxiolytic molecules interacting more specifically with the relevant receptors and as a result, these products should be free of many adverse effects of first-generation benzodiazepines [5].

These pharmacological successes are encouraging for the development of allosteric therapeutic tools in the case of other channel receptors such as calcium channels, NMDA receptors, and AMPA, the glycine receptor and the serotonin 5-HT₃ receptor.

Allosteric modulators of GPCRs (Receptors Coupled to G Proteins) should constitute in the near future a particularly successful, innovative pathway in the search for new and effective therapeutic tools [6]. The class of GPCR receptors represents in fact, nearly 200 identified receptors whose gene has been characterized. It is important to remember that 40% of current drugs are targeted at a GPCR. This is to say the physiopathological and pharmacological importance of these receptors and yet, if we note that we know for the moment only a minority of them (it should, according to the analysis of the human genome, there are more than a thousand!) the importance of these pharmacological targets should be even greater in the future. The vast majority of drug products that interact with GPCRs are classical agonists or antagonists competitive with their qualities, but also their defects related to their mechanism of action [7].

Can GPCRs lead to the development of allosteric regulators? The answer is again clearly positive, however, it is curious to note that the development of allosteric drug modulators has remained very limited until now. The first cause is that the complexity of these receptors did not facilitate the demonstration of their allosteric nature. The first

models proposed to account for the biochemical behavior of these receptors called for the existence of two conformational states of the receptor protein (coupled state and non-coupled to the G protein) [8]; Secondly, the new experimental results obtained forced us to extend this model to that providing for the existence of active and inactive conformations of the receptor in the absence of ligand [9]. This model supported the hypothesis of the allosteric nature of the receptor protein. It was then necessary to take into account the implementation of multiple states of the receptor that allowed its coupling to various G proteins [10]; the resulting model reflected the pleiotropy of such receptors, which could thus lead to the activation of distinct signaling pathways according to whether they coupled to this or that effector protein. Finally, even more recently, the notion of dimerization of these receptors forming homo or heterodimers (by combining with other GPCRs) has further increased the complexity of the allosteric mechanisms affecting this class of receptors [11]. The characterization of these mechanisms has made it possible to better understand the ability of GPCRs to intervene in an efficient and nuanced way in neuronal interactions, in particular in the fine regulation involved in the responses of the individual to stimuli, in the phenomena of adaptation, memory and learning neurons, in short, in all the elements that play a vital role in the physiological functioning but also in the central and peripheral pathological dysfunctions, especially in psychiatry.

Also, the development of pharmacological agents that are directly attached to the recognition sites of these allosteric regulators is very promising to obtain original and effective products: original insofar as the molecular targets concerned are still practically unexplored, effective in the as endogenous allosteric modulators discovered regulate receptors controlling essential functional activities, especially in psychiatry. The expected diversity of these endogenous regulators acting on distinct receptors favors a wide variety of therapeutic indications of the synthetic products that will be developed on the basis of these endogenous ligands.

Finally, it should be noted that the search for synthetic allosteric molecules is not limited to those that bind to sites specific to endogenous allosteric modulators; for a long time now, synthetic allosteric regulators have been discovered and implemented in an attempt to obtain therapeutic tools. A broad extension to various types of GPCRs but also to other allosteric proteins is currently in progress and should also allow having original molecules in their mechanism of action; an extreme diversity of their therapeutic indication can be expected [12].

In sum, a promising new era using the concept of allosteric modulators appears in the course of implementation in pharmacology. The advantages of allosteric drugs in terms of specificity, efficacy and reduction of adverse effects, combined with the very principle of their ability to regulate biological activities rather than block or constantly stimulate them, make these new molecules Potential actors of great interest that will lead to an evolution or even a revolution in drug therapy [13].

β -arrestins potential therapeutic targets in Alzheimer's disease (AD)

β -arrestins represent a small class of GPCRs regulators, which cause modulatory effects by facilitating the desensitization and internalization of GPCRs. This is another application of allosterism. Although beta-arrestins are known to be negative regulators of G protein-coupled receptor (GPCR) signaling, there is emerging evidence that they may possess additional functions as broad-spectrum accessory proteins that regulate G-protein receptors, intracellular traffic, and signaling. It has recently been proposed that a signaling complex associates with receptors with seven transmembrane domains, formed before reaching the plasma membrane, thus allowing signaling at other locations but also establishing another mode of regulation of the transport of these receptors.

Recent studies have shown that β -arrestin concentrations are correlated with amyloid- β peptide (A β) in the brains of Alzheimer patients and in animal models. β -arrestins increase the activity of

γ -secretase, which increases A β production and contributes to the pathogenesis of Alzheimer's disease [14].

Many studies concern the screening of compounds modulating GPR3 activity or beta-arrestin signaling in a mammalian cell and, in particular, compounds for the formation of beta-amyloid peptides. The invention also relates to inhibitors targeting β -arrestin signaling, pharmaceutical compounds and their use for treating so-called disorders [15].

Inhibitors of phosphodiesterase 10A

Inhibitors of phosphodiesterase (PDE10A) are the target of extensive research and efforts have been made to find them therapeutic targets. The researchers found that in murine HD models, cyclic AMP levels in the striatum are lower than in normal mice. This could explain why this region of the brain is particularly sensitive to the effects of Huntington's disease. Although neurotransmitters can send correct messages to the vulnerable cells of a brain with HD, the lower rate of second messengers could mean that these cells cannot interpret the information correctly. A Finnish scientific team led by Vahri Beaumont, was very interested in the evaluation of neuronal communication. Rather than waiting for neurons to die, these researchers argue that it is better to design tests for changes in how neurons talk to each other. Working with neural communication assessment specialists, Beaumont and his team have developed tests that accurately measure communications between neurons. After establishing these tests, they found that communication between neurons was significantly impaired in HD brains, particularly in the striatum, the most vulnerable area of the brain in HD. Their consistent conclusion is that vulnerable neurons in the striatum of HD mice are 'agitated' and too excitable [16].

Although the history of PDE10A is now more than 13 years old, it is relatively recent in terms of psychotropic development targets. Several pharmaceutical companies have developed clinical programs that attempt to validate the therapeutic potential of PDE10A inhibitors [17] the majority of firms focused on the treatment of schizophrenia in light of the observed preclinical results [18]. Indeed, these animal findings suggest that PDE10A inhibitors may have antipsychotic, pro-cognitive and positive effects in negative symptoms.

Epigenetic treatments in schizophrenia and cognitive disorders

Histones are at the center of epigenetic research [19]. These are proteins that wrap around the DNA, but when the histones are acetylated, portions of DNA are exposed, allowing the genes to function. The histone-DNA complexes, called chromatin, are constantly evolving, which does not make it possible to identify good or bad configurations. Everything is a question of balance, says the scientist and an imbalance can cause or aggravate an illness. But, if some portions of genes remain blocked due to lack of histone acetylation, then the genes may be "extinguished". Many studies have shown that impaired acetylation can be a key factor in neurodegenerative disorders such as Huntington's disease and Parkinson's disease.

A lack of acetylation of histones blocks the expression of certain genes. Researchers worked on postmortem brain samples of schizophrenics, managed to maintain postmortem DNA-histone interactions and were able to study histone alterations. Compared to healthy brains, brain samples from schizophrenic subjects show lower levels of histone acetylation in some parts that block gene expression. In young people with schizophrenia, this finding is much more pronounced [20].

On the basis of more pronounced results in young brains, treatment with Histone deacetylase (HDAC) inhibitors may be appropriate [21]. While current schizophrenia medications only treat certain symptoms, HDACs could effectively treat one of the causes of the disease in combination with antipsychotics [22]. Indeed it has been shown that chronic administration of atypical antipsychotics down regulates the transcription of the metabotropic glutamatergic receptor (mGlu2), an effect associated with the decrease of histone

acetylation in the human frontal cortex [23].

Peroxisome proliferator-activated receptors (PPAR)

Since the 1970s, fibrates have been prescribed in these dyslipidemic patients and have rapidly demonstrated their clinical interest. Originally, the mechanism of action of these drugs was not known. Over the years, research has been undertaken and knowledge has improved. It was in the 1990s that the target of these drugs was discovered: "Peroxisome proliferator-activated receptor or PPAR". These PPARs belong to a large family of proteins discovered a few years earlier: the "nuclear receptors", proteins of the cell nucleus acting as transcription factors. Further research on these proteins has led to a better understanding of metabolism, including that of lipids, which has broadened the therapeutic perspectives in the treatment of dyslipidemias, other metabolic diseases and in the prevention of cardiovascular risk.

Peroxisome proliferator-activated receptors are transcription factors belonging to the superfamily of nuclear receptors. Three subtypes of PPARs have been described in humans (a, NUC-1 also called b or d, and g) [24]. PPARs are involved in many biological processes including metabolic regulation, inflammation, apoptosis, and cell differentiation. PPARs are mainly expressed in neurons and glial cells. As in the case of any organ of the human body, brain activity is continuously balanced by homeostatic systems that modulate the main metabolic pathways through multigene regulatory programs [25].

The progressive discoveries of the broad and complex scope of PPARs have opened new perspectives for the treatment of neurological and psychiatric diseases. Three main therapeutic applications have been considered in psychiatric disorders [26]:

1. The reduction of inflammation
2. The modulation of neurotransmission
3. Metabolic regulation

PPARs exert a therapeutic action in inflammatory syndromes [27], including inflammatory processes that do not appear obvious in the clinical presentation of the disease, but are suspected to play an active but insidious role in the pathophysiology of the disease. In the brain, inflammatory processes may contribute to varying degrees to the establishment or maintenance of neurodegenerative mechanisms [25]. Such processes may be involved in various neurological diseases, but also in different types of major psychiatric disorders, including schizophrenia and mood disorders. PPARs, which appear to be widely expressed in neurons [28], could have a significant influence on both the spread and the cessation of such an inflammatory process. From this point of view, PPARs could be promising targets for different strategies in several psychiatric disorders including addiction problems [29].

Conclusion

In the future of therapeutics in psychiatry and neurology, in addition to the previously developed tracks, we can add what is now called personalized medicine [30]. If pharmaceutical companies enter this new vision of research that is personalized medicine, our drugs tomorrow will be very different. They will be "tailor-made" after analysis of our DNA, produced individually, with a much higher efficiency with minimal side effects. That will finally be very expensive, of the order of 15000 to 20000 euros per year and per individual. In fact, there are already drugs that fall into this development logic based on genomics. These are the monoclonal antibodies, some of which are already prescribed. But within 10 years, DNA chips will become commonplace in analytical laboratories and medical practices and it will become possible, for a growing number of diseases, to design or adapt drugs according to the patient's genetic profile. However, this medical revolution, if it is full of hopes for the sick, also carries heavy uncertainties in the care and adaptation of our health system. The generalization of these new "tailor-made" medicines, with very high added value, requires a profound change in our entire healthcare system and its methods of financing and administration. Today the

respective shares of drugs and hospital in our health system are 20% and 45%. But tomorrow this report will inevitably reverse, which may cause socioeconomic changes very difficult to manage. In this perspective, telemedicine can play a major role and constitute a very powerful tool of adaptation to facilitate the necessary mutation of our health system under the effect of these scientific and medical advances.

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