Schizophrenia and psychosis-related disorders: how the glutamate hypothesis contributes to the onset of the mental illness

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Abstract

Schizophrenia and psychosis in general, are health problems for a lot of patients around the world. The causes of developing those mental illnesses are still unknown. Several hypotheses have been introduced to justify these malfunctions. Our article focuses on the glutaminergic hypothesis and how it might lead to the onset of the disorders. The NMDA receptor controls the release of acetylcholine, GABA, and dopamine, while at the same time, it downregulates the 5HT1A receptor and upregulates the 5HT2A. While NMDA antagonists can produce psychosis, NMDA agonists might have the opposite effect. To that end, we found a ligand called 2-Phenylcyclohexane-1-carboxamide and studied its pharmacological properties through the use of the program mcule. What we found was an affinity for the NMDA receptor, the GABA transporter, and acetylcholinesterase. We urge researchers to study further this particular molecule in hopes of identifying all possible in silico interactions and measuring their respective Kds.

Introduction

Glutamate(Glu) is one of the key neurotransmitters that have stimulant effects on neurons, through their respective receptors. The most studied Glu receptor is the NMDA. One of its ligands is Phencyclidine (PCP), a well-known selective NMDA antagonist, which causes a phenotype that closely resembles schizophrenia and the symptoms that occur subside after sufficient clearance of the drug from the bloodstream. Also, some interactions of PCP involve the α2 receptor, though there is not substantial evidence to demonstrate the effects on the phenotype. What’s more, it has been suggested by other authors that the PCP binding site 2 and the α2 binding site are the same. [1] Though, it has been demonstrated that PCP acts in major, at the NMDA receptors, an affinity for the D2 receptor has also been shown. Thus, the NMDA decreased activity contributes to the increase in DA activity. [2] After all, the effect on the dopamine D2 receptor(D2R) is measured when a high dose of PCP is present. For the most part, the psychotic-like features of PCP are dose-dependent and more likely to occur in low doses and begin to potentiate its effects with the increase in dosage. That was the basis for the Glutaminergic hypothesis.

In history, many researchers have studied the physiology of sleep. An increased prefrontal cortex(PFC) activity tends to occur during sleep induction, which is later reversed in the REM sleep stage. In particular, the dorsolateral prefrontal
cortex tends to 'turn off' and the authors suggest that this is but the result of direct inhibition from acetylcholine(Ach) neurons, which are most active during REM sleep. [3] But how do sleep patterns collerate with the glutaminergic hypothesis? One key aspect is that Glutamate receptors are less active during psychotic episodes and the patient receives less sleep, which may go as far as a week without sleep. During that period, the patient is more prone to hallucinations and delusions, as noted by an experiment in healthy individuals; [4] The immediate conclusion from this endeavor is that Ach levels drop, thus reducing the ability of the Ach neurons to inhibit the PFC. But, during schizophrenia the PFC is generally less active, so how can one contradict the other? Well, presynaptic NMDA receptors tend to stimulate Ach release, suggesting that Glu activity is crucial for overall sleep deprivation, despite seeming like a paradox. [5] Ach seems to be lower in cortical regions, during psychosis, given the colleration of the nicotinic cholinergic system with cognition, thus it is safe to assume that reality distortion and Ach depletion are key characteristics in schizophrenia and psychosis-related disorders. [6] Therefore, the Glutaminergic hypothesis, supports that the depletion of Glu, affects other neurotransmitters as well, both positively and negatively, depending on the type of neuron, either inhibitory or stimulant, as well as the location of the receptor, either presynaptic or postsynaptic. After all, it's not just Ach that its release increases, but DA as well, with the collation that DA activity is increased by NMDA antagonists, such as ketamine. [7] This pinpoints the fact that the prone dopaminergic action of PCP is merely mediated through the antagonism of NMDA, even though it is speculated that higher doses of PCP show an affinity for the D2R. Even serotonin(5HT) is also affected by NMDA activity since the 5HT1A receptor tends to cause downregulation of the NMDA. [8] Moreover, cannabidiol(CBD) a well-known antipsychotic, among other properties, tends to show agonist properties for the 5HT1A [9], the same receptor that causes downregulation of the 5HT2A receptor. As mentioned, in the quoted article, there is significant interaction between the NMDA, the 5HT1A, and the 5HT2A, since the 5HT1A tends to downregulate the rest, as an inhibitory receptor. [10] Overall, when stimulated, the NMDA receptor increases Ach, increases DA, when inhibited, and is downregulated by the 5HT1A. A more plausible case is that memantine, a drug used for later stages of dementia, is an NMDA antagonist and acetylcholinesterase(AchE) inhibitor. This suggests that, in neurodegenerative diseases, the increase of DA and Ach, are crucial for halting the progress of the disorder. [11] As the citation quoted mentions, memantine's prosthetic actions [12], compared to those of selective NMDA antagonists, halt the delirium effects. The blocking of nAchRs due to memantine is considered a drawback since it decreases cognitive function, thus the creation of nAchR agonists might be more beneficial. It should be noted that, through the clinical studies of memantine, it is presumed that Ach increased release tends to bypass the NMDA antagonist effect and thus the psychotic features, which might be a good trick when creating novel medicine for psychotic features.

DA and Glu have a complex set of interactions. According to the cited article, the dopamine D1 receptor excites the NMDA activation, whereas the D2R has an inhibitory role. The activation of the D1 receptor involves the prefrontal cortex, the globus pallidus, and the striatum, whereas the D2 receptor involves the striatum and the midbrain, in general. The NMDA receptor, in turn, excites the release of GABA in the striatum and the globus pallidus, probably as an offset to the stimulant role of the NMDA. The D2 receptor, on the other hand, has the opposite role, being inhibitory. [13] The 5HT interactions with the NMDA involve mainly the 5HT1A and the 5HT2A, which are located in the prefrontal cortex.
in ample amounts. It seems, that agonists of those receptors, in absence of the NMDA, caused a decrease and increase in PFC action potential, only in high concentrations, whereas the presence of NMDA, decreases the action potential of the 5HT1A agonist and increased that of the 5HT2A agonist. In both cases, the low concentration of those agonists failed to produce an action potential, suggesting that the NMDA receptor is crucial for enhancing the effects of their respective agonists, possibly via ion channels, since the NMDA controls ion permeability.\textsuperscript{[14]} As noted previously, the 5HT1A receptor downregulates the NMDA. The opposite phenomenon is speculated to occur between the NMDA and the 5HT2A, given their synergistic potential. Also, 5HT1A downregulates the 5HT2A/C as well, suggesting that those 3 receptors have a contradictory role, between them.

Since the NMDA amplifies the effects of ion-gated channels, it is presumed that the nicotinic cholinergic system and the NMDA cooperate, to control the excitability of neurons. The α7nAchR seems to increase NMDA activity, in the nucleus accumbens and the hippocampus, as shown by the use of respective agonists choline and nicotine. However, selective α4β2 agonists did not have the same properties.\textsuperscript{[15]} Despite that, the glutaminergic hypothesis seems to exist even with a low dose of PCP, at 2-5mg, where the first changes in perception tend to occur. This suggests that NMDA alone can incite psychotic episodes. Going one step further, we assume that Glu is the catalyst in psychosis since the deficiency in the action potential of Glu receptors tends to initiate symptoms that resemble those that we get from an excess of DA in the limbic system. Of course, NMDA antagonists increase DA activity indirectly, thus the result is the same. It is far safer to estimate that there is not one way to produce a psychotic episode, however, it takes a genetic predisposition to establish the break from reality, since few patients treated with PCP or ketamine, reach the point of acquiring a diagnosis or having relative symptoms.\textsuperscript{[16]}

Thus, research should focus on identifying the intracellular malice that makes psychosis irreversible. However, our manuscript does not focus on the genetic components of the disease but rather on the receptor abnormalities that accompany them. To that end, we tried to produce ligands that may prove beneficial to the future of patients with psychotic-related disorders.

Methods: To that end we used the program mcule, to study the affinity of a certain ligand called 2-Phenylcyclohexane-1-carboxamide, with the results shown below.

Results
This is the result for the affinity with the NMDA receptor subunit zeta-1, which was measured to be \(-7.6\) (high) of Rattus norvegicus at the \((x,y,z)=(5,6761, 37,8899, -16,928)\). Also, the ligand showed an affinity for the AchE of Mus musculus, measuring at \(-7.5\) (high) at the \((x,y,z)=(20,6367, -13,604, -36,0402)\). Also, it showed an affinity for the GABA transporter of E.coli measuring an affinity of \(-6.9\) at the location \((x,y,z)=(35,1802, 56,1118, 30,06970)\).
Those results highlight the fact that this ligand might have similar properties to other stimulants. For instance, the ability to increase the release of Ach, suggests that it could be used as an alternative for AchE inhibitors, such as those used in dementia or bowel syndrome disease. Also, since it does cross the blood-brain-barrier, it is presumed that it could replace nicotine, as a substance of abuse, with the difference that it is not to be inhaled or chewed, but given as a tablet, the same as other stimulants targeted for attention deficit and hyperactivity disorders (ADHD).

Moreover, if it is an NMDA antagonist, chances are that it might induce psychotic episodes or akathesia, the same as PCP, in a dose-dependent manner. In that case, it might be useful for researching psychosis. In case, it is an agonist, the opposite is prevalent since PCP can induce psychosis at a very low dose, acting as a selective antagonist of the NMDA receptor. That is why we urge researchers to study this molecule's pharmacology, hoping to alternate the basic theorem of treating psychosis-related disorders.

The effect on the GABA transporter, suggests that it might also have anxiety relief abilities, and in higher doses, it might produce sedation. Of course, the fact that it is a non-selective ligand indicates that the dose is crucial for determining the phenotype.

Discussion

All in all, 2-Phenylcyclohexane-1-carboxamide might be a potential ligand for the treatment of schizophrenia and psychosis-related disorders, based on the glutaminergic hypothesis. What we assume is that for an unknown reason, Glutamate activity drops, mainly in the limbic system and this produces a spike of DA in the same areas, such as the amygdala and the striatum. At the same time, the 5HT1A receptor is dysregulated, which is a paradox, considering that many antipsychotics block the 5HT1 receptor, and the 5HT2A is upregulated, same as the NMDA because they are out of control of the 5HT1A. Also, due to the glutamate hypo-activity, the action potential of nAchRs is reduced, producing an anticholinergic effect. We suggest that an active, but not too potent agonist of the NMDA receptor, might cause increased release of Ach, and at the same time, decrease DA activity in the limbic system. Moreover, this ligand should have combined properties of 5HT1A agonist and 5HT2A antagonist, since the 5HT2A and NMDA have synergistic effects. Last but not least, it should be tested whether the NMDA agonist alone could control DA spikes, or whether dopamine receptor antagonists be introduced to enhance the effects of the former.

References


