Research Article

Dopamine D5 receptor involvement in LTP and LTD: adjustment to the dysconnectivity theory of schizophrenia

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The purpose of this article is to emphasize the role of the dopamine D5 receptor in the pathophysiology of schizophrenia, through its actions on the hippocampus, the prefrontal cortex, the striatum, and the basal ganglia. We believe that this receptor, along with other key receptor systems, mainly the 5HT2A/C, the GABA(A), the NMDA, and some nAchRs are vital for long-term potentiation(LTP) and long-term depression(LTD) effects, that control the plasticity of the brain. We assume that the anatomical and physiological traits that have been found, show us a loss of plasticity, which may be intertwined with a degree of atrophy in the brain, noted in a percentage of schizophrenia patients, as a loss of grey matter. Of course, the plasticity is mediated by different receptors in each brain region, and the tissues associated with the dopamine D5 receptor, show us a multi-parameter function, through the LTP and LTD. The effect that the dysfunction of the LTP and LTD has on the brain, is related to the dysconnectivity between parts of the CNS, a trait associated with many neurodevelopmental disorders, especially schizophrenia.

Introduction

1. The dysconnectivity theory and plasticity of the CNS

The involvement of the D5R in schizophrenia has been poorly established, even though dopamine is crucial for the pathophysiology of the disease. To better understand this phenomenon, we have to take into consideration the functions of the D5R in each brain region, that it is linked to, explore its pathway, as well as the interactions with other key receptors, such as the 5HT2A or the D2, some of the most well-studied components in the schizophrenia disorder. In any case, we speculate that D5R

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dysregulation is one of the key aspects of the dysconnectivity theory. The mechanism via which D5R is dysregulated is not known. The dysconnectivity theory supports that there are certain pathways between circuits, that help transmit a message from one region to another, thus building up a communication network. These pathways are dopaminergic, GABAergic, or glutaminergic. Each of those is interconnected with a specific part of a circuit, meaning it serves a specific function. The loss of this 'network', causes abnormal transmission in several parts of the CNS. One such example is the activity of the striatum during a psychotic episode, given that the striatum detects and gathers all types of sensory information. The reduction of activity of those pathways leads to failure of synchronization, in terms of transmission, and thus alternations in receptor expression. This disrupts the long-term potentiation-long term depression balance and thus brings about a loss of plasticity. These points serve as an introduction to the purpose of the article.[1]

2. D5R functions intertwined with the hippocampus anatomy

Dopamine D5 receptor (D5R) is located in a lot of regions, such as the hippocampus, the amygdala, the prefrontal cortex, or even the striatum, and is more prevalent than the D1R, in the entirety of the CNS. D1R/D5R mediates the processes of the hippocampus that are related to different types of long-term and short-term memory, reward signals, learning, and increasing the synaptic plasticity of the region. The D5R pathway seems to control, through the activation of its G-protein, the activity of the nuclear factor cAMP-response element-binding protein(CREB), with the help of signaling agents, such as phosphatidylinositol 4,5 diphosphate (PIP2), phosphatidylinositol 3,4,5 triphosphate(PIP3), protein kinase C (PKC) and Akt. D1R shares the same final agent/target, through a different pathway, which is not to be analyzed in detail. However, this is vital for D1-like receptor interactions, since both GPCRs are categorized as Gs, which means that they increase cAMP activity, the opposite effect of D2-like receptors(D2, D3, D4).[2] Moreover, since the hippocampus, through long-term potentiation(LTP) and long-term depression(LTD), can connect memories with certain behaviors, such as stress, fear, and drive, we can perhaps assume that the manifestations of schizophrenia may require the involvement of this element, to establish long term 'paranoid' behavior. The hippocampus is one of the CNS regions, that can associate certain stimuli, with thought patterns, thus bringing about an associative thought process, that is the main drive of delusions. As for the main supplier of dopamine (DA) to the hippocampus, it seems that the ventral tegmental area(VTA) plays that role, without

excluding other areas such as the retrorubral area A8 and the substantia nigra pars compacta A9(SNpc). It appears that the axons from where DA arrives to the hippocampus, determine the type of activity, the latter (hippocampus) would be engaged. Note that, this activity refers to the interpretation of the memory through the LTP and LTD systems. It has been described, that antagonism of the D1R/D5R brings about a distortion to the LTP, thus the processing of information, related to memory. There are subtypes of LTP, mainly E-LTP and L-LTP, each one of them being linked both to receptor pathways and the areas, where the antagonism of the D1-like receptor occurs. From those findings, the authors suggest that the inhibition of LTP, due to the referred antagonism, might determine whether a memory is worth being stored or forgotten. Similarly, LTD is also important. LTD and LTP work together to determine the processing of memories. Again, there are two subtypes, E-LTD and L-LTD, both being vulnerable to D1-like receptor antagonism. However, both in LTP and LTD, the type of the signal that affects the D1R and D5R is measured in duration and affinity, since it is believed that the activity of those receptors is elevated or weakened, to create a better optimization of the process.[2]

3. D5R and inflammation

One of the aspects of the function of the D5R is its involvement in the downregulation of NADPH oxidase, angiotensin type 1 receptor (AT1R), and the reduction in oxidative stress.

In the current article, the authors Zhiwei Yang et al, performed an experiment with wild-type mice and mice that were knockout for the D5 gene wild type, that instead carried a well-known mutation of the D5 gene, that was associated with the decreased response of the D5R to D1-like receptor agonists. This mutation is known as hD5F173L. The methods used, involved the CHO cell transfection, through the use of the pcDNA6/V5-His vector and LT1 reagents. The verification of the transfection was tested via immunoblotting for His/V5 presence. Cell cultures developed in the presence of phorbol 12-myristate 13-acetate, 3-isobutyl-1-methylxanthine, and fenoldopam. The oxidation of 2',7'-dichlorodihydrofluorescein diacetate was used to measure ROS in all CHO cells. To measure blood pressure, mice (C57Bl/6) were fed a normal NaCl diet for 14 days that was changed to a high NaCl diet for 15 days, and then injected intraperitoneally with candesartan. NADPH oxidase activity was measured by NADPH-induced chemiluminescence with lucigenin and NADPH. The samples were

immunoblotted with anti-Nox2, anti-Nox4, and anti-AT1R antibodies and then tested for glyceraldehyde-3-phosphate dehydrogenase (GADPH).[3]

The result was an increased response to Candesartan, an AT1R inhibitor, with NADPH oxidase regulation properties, but only in the mice carrying the mutated gene. Apart from the results, that collerate with increased blood pressure in mice carrying the mutation, it appears that the D5R is a regulator of reactive oxygen species (ROS), through the inhibition of the NADPH oxidase. This suggests that in schizophrenia, there is some degree of susceptibility to ROS, due to the dysregulation of the D5R. This is evident through the case reports of inflammation, noted in schizophrenia patients. This sometimes is a result of an infection, mostly viral, but other times it is a result of diseases of the cardiovascular system, that the patient is suffering from.[3]

There are several gene components, mainly expressed in immune system cells, that co-align with increased pro-inflammatory responses. This makes patients with schizophrenia vulnerable to various illnesses and infectious diseases, such as autoimmune disorders or even covid-19. The effect of excessive inflammation in the brain is interwoven with the midcortex and the striatum. The findings are contradictory but give a clue to the way that inflammation, if chronic, leads to exacerbated negative symptoms.[4][5][6]

4. FMRIs of patients with schizophrenia

Numerous fMRIs, have reported disturbances in the frontotemporal, fronto-cortical, and cortical-cortical interactions. FMRI has been recently evaluated as more detailed and accurate than the PET scan, in terms of assessing the condition of the patient, suffering from a mental disorder, according to the authors Ruben C. Gur et al . Apart from the dysconnectivity theory, which is the main distortion taking place in schizophrenia, fMRIs have shown abnormalities in nuclei circuits as well. This is intertwined with the reduction in volume, the asymmetry between left and right hemisphere function, and decreased or exacerbated correspondence to certain stimuli. This takes place across a lot of complexes of nuclei, such as the hippocampus or the amygdala, and is most studied in the case of the temporal lobe. Note that there is no single circuit responsible for the entirety of symptoms, despite the speculation that some tissues are crucial, though not determining factors, for the presence of a spectrum of symptoms. Such a case is the association of striatum hyperactivity with the prevalence of positive symptoms, during a psychotic episode. Certainly, based on the definition of schizophrenia as

a perception disorder, we could estimate that it is strongly linked to cognitive deficits, over the distortion of senses. More important than that, it is a neurodevelopmental disorder, that is manifested in its purest form, after the completion of the development of the CNS. This collerates with the claim that it should be considered as a multi-parameter, long-lasting combination of disorders, not just one disease. After all, since there is heterogenicity among patients, the fact that there is a spectrum, rather than a single phenotype, justifies the term 'set of disorders.[7][8]

5. D5R and other neurotransmitters controlling plasticity

5.1. 5HT and D5R

There has been noted, an interaction between different transmitters and dopamine. We believe that this extends to all dopamine receptors, across different anatomic brain compartments. The most studied system of interaction involves the serotonin system (5HT). In this article, we attempt to focus on the effects of the D5R. DA and 5HT seem to have both synergistic and opposite effects, depending on the type of the region, they act upon. In the hippocampus, it is mentioned that 5HT plays a key role in memory and emotion regulation. Note that the hippocampus is divided into 5 regions, the dental gyrus (DG), which is the main entry to the region, the CA1, CA2, CA3, and the subiculum. In those sub-compartments, their common receptor is the 5HT2A/2C, which is strongly associated with schizophrenia. The 5HT7, the antagonism of which, has antidepressant properties, is also linked. [9] 5HT2A is debated as to whether it has inhibitory or stimulating properties. However, it has not yet been clarified. As for the 5HT7, it is estimated that it exerts its effects on GABA neurons, but this is yet to be decided, as the use of 5HT7 agonists has both an inhibitory and a stimulating profile. In all of those regions mentioned, the D5R is predominant, therefore we assume that there is a link between the 5HT7, and 5HT2 interneurons, and the D5 receptor. This link remains elusive, for the time being. In any case, the inhibition of SERT appears to be a non-specific mechanism, when it comes to pro-cognitive effects.[10] Apart from the hippocampus, there are other regions, where the 5HT and DA interact, an example of which is the resting-state networks(RSNs). These include the sensorimotor network (SMN), salience network (SN), and default-mode network (DMN). There has been noted an imbalance in those regions, in case of psychiatric disorders but the review we cited, studies this phenomenon in healthy individuals. Given that there are projections of pure dopaminergic and

serotoninergic pathways on the RSN, we can understand how one impacts the other. For instance, the substantia nigra pars compacta are connected to SMN, the VTA to the SN, and the raphe nuclei to the SMN and DMN, respectively. DA appears to increase plasticity, in the SMN and SN and decrease the DMN. 5HT has the opposite effects, though it's noted projection, to the SMN and DMN. The SMN-SN and the DMN seem to coordinate and compete for dominance, according to the signaling they receive from 5HT and DA. From that evidence, it is highlighted that the disruption in DA and 5HT activity, leads to an imbalance in RSNs and an altered activity network, that is adjusted to the signaling of those transmitters.[11] It should be noted that the first suspicions around the 5HT system were raised, due to the hallucinogenic effects of LSD(D-lysergic acid diethylamide) and psilocybin(psilocin is psilocybin's active metabolite). Those were 5HT2A partial agonists and agonists, respectively, but had minor effects on other 5HT receptors as well. Specifically, LSD acts on the 5HT2A, 5HT2C, and 5HT1A, regarding the serotoninergic system. Also, in the dopaminergic system, it is considered a D1R, D2R partial agonist, and a D4R full agonist. Interestingly enough, it also increases the activity of the NMDA subunit NR2B, in the prefrontal cortex. Moreover, the TAAR1 receptor(trace amine-associated receptor 1) is involved and it appears that it is crucial for the induction of psychotic-like features, through the VTA.[12] As noted above, the D5R interacts mainly with the 5HT2A and 5HT2C, so an effect that is mediated via the prefrontal cortex or the VTA, or via their respective projections could enhance a psychotic state.

5.2. Ach and D5R

Another neurotransmitter affected by the D5R is acetylcholine. D5R mediates the release of acetylcholine(Ach).[13] Moreover, knockout D5R mice appear to have a reduction in the Ach levels, in the same region. That clarifies the importance of the receptor.[14] To better understand this case, we have to establish the main fact, that sometimes, Ach can be derived from projections of neurons, that have cholinergic properties too, but belong to other types of nuclei. Apart from the hippocampus, the DA-Ach balance is evident across the whole striatum, such as, in the case of the basal ganglia, whose disruption of function, along with the involvement of the substantia nigra pars compacta(SNpc) leads to Parkinson's disease(PD). Cholinergic interneurons in the striatum can be divided into tonically active neurons(TAN) and phasically active neurons(PAN), the difference which, lies in the frequency of firing. The TAN is the most affected by dopamine depletion, as seen by the use of dopaminergic antagonists, such as MPTP and haloperidol, through experiments in monkeys. Despite such a finding,

the interactions of the DA and the Ach remain unclear, given that DA receptors are mediated in terms of activity, through the mechanism of motive/desire, whereas the cholinergic interneurons don't have the same response. Therefore, the authors investigated the pause phase of TAN, to better explain this. The pause phase of the TAN is controlled by the D2 receptor, through the frontal cortex and the thalamus. The D5R is involved in the LTP and LTD processes, due to the actions of localized nAchRs and GABA receptors, with the nAchRs giving the signal to the TAN, to fire. Therefore, while the D1R appears to prolong the pause phase, D5R seems to increase the activity of TAN. The unbound postsynaptic nAchRs and mAchRs are the cause of the pause response in TAN cells. While this is contradictory, it appears that despite the high tolerance of the nAchRs to nicotine, after prolonged use, the DA receptors have increased response in high frequencies, but decreased, in low frequencies. Thus, it is safer to claim that this pause phase leads to increases in DA activity(usually), whereas the Ach binding to the nAchRs and mAchRs leads to the exact opposite phenomenon, which is the reduction in DA response (through D1 and D2 receptors) and the activation of the TAN(mediated by the D5R). Therefore, Ach and DA work cooperatively, but in different phases of the function of TAN.[15] In any case, we see why the dysregulation of the D5R leads to DA-Ach imbalance, at least in the area of the striatum. It should be noted that there is also a colleration between nAchRs and DA, given the effects of nicotine on the dopaminergic system, where the nicotine addiction is manifested. First of all, nicotine increases DA activity in the VTA, thus enhancing DA projections from the VTA and the plasticity of the mesocorticolimbic pathways, in general. Other projections that are optimized, through the use of nicotine, include the prefrontal cortex, the striatum, as well as the substantia nigra pars compacta.[16] Colleration with the nAchRs and nicotine is highly important, given that 90% of schizophrenia patients are heavy smokers, indicating a connection either between antipsychotic medicine and nicotine or schizophrenia and nicotine. According to the study we cited, it appears that nicotine has cognitive-enhancing abilities, as noted above, and cognitive decline is exacerbated, after quitting smoking.[17]

5.3. GABA(A)R and D5R

Another interaction of the D5R involves the GABA(A) receptor. This interaction takes place in the hippocampus, as evidence shows. GABA(A)R is highly regulated by D5R, which might be the link between the pause phase of TAN and the receptors, whose activation leads to this response. To be specific, it appears as if, the D5R stimulation leads to the GABA(A) inhibition, to allow the TAN to fire.

The exact opposite occurs during the pause phase of TAN, when the D5R is inactive, whereas D1R promotes nAchRs and GABA(A)R actions.[18] Also, in the substantia nigra, there is a release of DA, as well as GABA, both important for the REM phase of sleep. This region projects on locus coeruleus (LC) and pedunculopontine tegmentum (PPT), areas that are important for REM. An association between Parkinson's disease(PD) and loss of dopaminergic neurons in the substantia nigra, has been established which often co-aligns with disturbances in sleep patterns. Another disease that has been linked is also depression. Note that, in schizophrenia, there is often a lack of sleep for days on, during the onset of psychotic episodes, thus there might be an indication that DA activity in the substantia nigra is decreased and that GABA-DA balance is disrupted. That is why, the use of benzodiazepines, as support treatment in psychotic episodes, helps re-instate sleep patterns and reduce anxiety.[19] Another topic that GABA is involved in, is tardive dyskinesia, induced by antipsychotics, mostly in the first generation(neuroleptics). It is not only GABA and DA that are linked since it has been found that there is an increase in cholecystokinin and opioids in the striatum. Also, neurotensin, neuropeptide Y, substance P, and somatostatin concentrations are altered, due to the presence of neuroleptics. Both evidence combined, suggest involvement of several factors in extrapyramidal symptoms.[20] In that case, the induction of GABA(A) agonists or GABA transporter inhibitors might help alleviate some of the extrapyramidal symptoms, as well as help, restore sleep patterns and stabilize the patient.

5.4. D5R and Akt, BDNF expression

It appears that the D5R located in the prefrontal cortex is responsible for the upregulation of the Akt and BDNF. This perhaps is relevant to the cognitive decline which is present in schizophrenia, since the hypofrontality mentioned in the disease, leads to distortion of the D1-like receptors. Whereas the present studies focus on the development of D1R selective agonists, we should also take into consideration the chances of D5R involvement. After all, the BDNF is a neurotrophic factor, allowing for neurogenesis, to take place.[21]

6. Memory interval and hippocampus

The most prominent evidence of memory distortion in schizophrenia occurs as a misinterpretation of time, such as the sequence of events, the duration of them, or even the content of memories. This is more prevalent in the psychotic phase of the disease, but a long-term cognitive decline would

eventually reproduce the same results. The authors mention that the type of time duration interpretation is controlled by different parts of the brain. Patients with schizophrenia appear to have a disruption in that process, both the ones suffering and their offspring. This suggests a possible genetic marker as evidence of risk to the disease. The authors collerate the upregulation of the D2R in the striatum area, especially in non-treated patients, with the fact that they may affect the prefrontal cortex, through hypofrontality. They proceed with linking several parts of the striatum to this hypothesis, such as the basal ganglia, but the findings remain elusive since there is no clear evidence pointing to the source of the disorder. To further prove this approach they use mice with the overexpression of D2R in the striatum, which in most cases led to hypofrontality. Despite that, the authors appear to have phased a dilemma, as to whether the decline is present-due to cognitive impairment or loss of motivation. The first one is linked to the cortico-striatal area, whereas the second is linked to the limbic system.[22][23] Through the use of time interval tests and antipsychotics, it appears that the D2R is the most prominent factor, determining cognitive impairment, associated with working memory and time perception.[24]

Despite such evidence, we have to disagree with the above notes, given that, as the authors Peter D Balsam et al, stated, the time perception field and the brain, is not been substantially discovered, thus there is a lack of evidence to further determine which type of tissue is responsible. Through the findings above, we suggest that the striatum is not the only part taking place in the process, since the hippocampus is also related. The hippocampus belongs to the limbic system and is associated with the striatum and the prefrontal cortex and the authors fail to consider all three. The link is established through frontotemporal pathway circuits, such as the frontostriatal pathway.

7. Hippocampus pathoanatomy in schizophrenia

The first link that is to establish, concerns any anatomical or physiological changes in the hippocampus, in patients with schizophrenia. Clearly, the authors state that the following disruptions have been reported: increased right/left volume asymmetry, general volume reduction, subfield volume reduction, dysconnectivity with other CNS parts, incomplete inversion patterns, and morphological inward deformation. Some of those abnormalities are linked to pregnancy, despite the lack of evidence, to determine the exact period of this distortion taking place. The only clear suggestion is that, since it is a neurodevelopmental disease, these phenomena could take place anytime, before the completion of CNS development. The decrease in hippocampal volume is mostly

associated with the CA1 and CA2 areas. As to the causes, the authors do not exclude a case of inflammation, as reported in the introduction section.[25]

8. Receptor alternations associated with the hippocampus, the prefrontal cortex, the striatum, and the basal ganglia

The second link is in terms of receptor deviations. First and foremost, D5R is located in many regions, including the prefrontal cortex, the basal ganglia, and the limbic system, in general. Thus, we have to look out for receptor abnormalities in all of those. For the most part, as established through the introduction section, the 5HT2A is highly associated with schizophrenia and most atypical antipsychotics tend to block this receptor, either through antagonist or inverse agonist properties, as is the case with risperidone and olanzapine, two of the most prominent first-line antipsychotics, when it comes to full-blown schizophrenia/psychosis.[26][27] Little is known about the 5HT2C and most antipsychotics tend to not block this receptor. In another article, the authors suggest that 5HT2C decreases dopamine transmission, whereas the opposite takes place through 5HT3. Of course, this occurs in different ways, across all brain regions and further analysis needs to be performed.[28] Given the prevalence of the 5HT2A/C in the hippocampus, we can assume that it is possibly linked to LTP since the evidence shows that the 5HT2A is linked to LTP, associated with the prefrontal cortex and we may assume that the same goes for the latter[29]. Since, the 5HT2 are the main mediators of DA release[30], through the 5HT system receptors, some articles tend to associate the effects of 5HT2, by affecting glutamate and GABA (on the prefrontal cortex), GABA (on the NAc), dopamine and GABA (on the VTA). All in all, dopamine release is exacerbated in the mesolimbic system and the NAc but is decreased in the VTA and the prefrontal cortex, through the actions of the 5HT2A/C.[31] Taking that into account, we can assume that the hippocampus, which belongs to the limbic system, tends to be increased in activity, by the actions of the 5HT2. An interesting fact is that both 5HT2s tend to be downregulated when being blocked by antipsychotics, antidepressants, and 5HT2 blockers.[32] This is because postsynaptic 5HT2A, and possibly 5HT2C too, are mediated as to their effects, by other 5HT receptors.[33]

In terms of GABA, it appears that a higher percentage of GABA concentration in the hippocampus is evidence of a higher chance of retrieving information when it comes to cognitive tasks. GABA has negative effects on the LTP, as proved by the use of GABAR antagonists, which tend to increase LTP properties, mediated by glutamate. Glutamate is essential both for LTP and LTD. GABAR agonists tend

to decrease these cognitive processes, as shown by the use of benzodiazepines, which tend to affect memory, in higher concentrations.[34] Given the association of GABA to the prefrontal cortex, the VTA, and the NAc, we expect that the glutamate hypothesis, which is linked to schizophrenia, might bring about a loss of healthy synaptic connections, as proven by the use of NMDA antagonists, which in fact, tend to resemble schizophrenia symptoms.[34] Also, the nAchRs participate in the plasticity process of the hippocampus too, as shown by the use of nicotine.[35]

This dispersed information all leads to a general hypothesis. It seems that in schizophrenia, the 5HT2A/C tends to be blocked and downregulated by antipsychotics, leading to lower levels of dopamine release. Also, the D2-like receptors are blocked as well(by antipsychotics), to mediate the limbic system's excessive response, during a psychotic episode. This affects the hippocampus as well because 1) there is dysconnectivity with other CNS parts 2) there are abnormalities in the firing of receptors, associated with the asymmetrical volume between regions 3) there is the phenotypic loss of cohesion of memories or the formation of false memories, which co-align with each other.

However, since the D1R is upregulated because of the hypofrontality, the same may occur through the D5R, as an effort to reverse CNS receptor abnormalities, associated with schizophrenia.[36] Despite that, the evidence does not show increased signaling towards those receptors. This suggests, that DA does not bind to the D1-like receptors efficiently and the upregulation of them is done to increase transmission.

Conclusion

The key components affecting the hippocampus are the nAchRs, the 5HT2A/C, the D5R, GABA(A), and NMDA receptors. Through this analysis, we explain how these systems support one another to bring about stability to the hippocampus and other CNS regions, where the D5R is involved, and due to the disease those regions tend to be dysregulated. There are some aspects of antipsychotics and other psychiatric medications, that tend to downregulate receptors, that are vital for the function of the hippocampus, and findings on whether chronic schizophrenia, treated with antipsychotics, shows an elevated hippocampal activity or the opposite, remain contradictory. In the case of untreated psychosis, however, the hippocampus tends to be dysfunctional, due to the dysconnectivity with other parts of the CNS. To restore the connectivity between parts of the CNS, it is proposed to use antipsychotics that, among the classic D2-like antagonist and 5HT2A inverse agonist effects: 1) are

α4β2&α7 nAchR agonists[37] 2) D1-like receptor agonists, as is the general trend, considering that there is an upregulation in those receptors, but no substantial differences in signaling towards them.

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