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

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Abstract

The purpose of this article is to emphasise 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 5HT_{2A/C}, the GABA(A), the NMDA and some nAChRs are vital for the long term potentiation and long term depression 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, per se. . 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, though the LTP and LTD, of course. 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. D5R functions intertwined with the hippocampus anatomy

The involvement of the D5R in schizophrenia has been poorly established, despite the fact that 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 5HT_{2A} or the D₂, some of the most well studied components in the schizophrenia disorder.

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. D1R/D5R mediate the processes of the hippocampus that are related to different types of long-term and short-term memory, reward signals, learning and increasing of 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 analysed in detail. However, this is vital for D1-like receptor interactions, since both GPCRs are categorised as Gs, which means that they increase cAMP activity, the opposite effect of D2-like receptors(D2,D3,D4). Moreover, since the hippocampus, through long term potentiation(LTP) and long term depression(LTD), is able to connect memories with certain behaviours, such as stress, fear, drive, we can perhaps assume that it's possible that the manifestations of schizophrenia require involvement of this element, to establish long term 'paranoid' behavior. In fact, the hippocampus is one of the CNS regions, that is able to 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 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 an 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 worthy to be stored or forgotten. Similarly, the 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, so as to create a better optimization of the process.^[1]

2. D5R and inflammation

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

In the current article, the authors Zhiwei Yanget 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 decreased response of the D5R to D1-like receptor agonists. This mutation is known as hD5^{F173L}. The methods used, involved the CHO cell transfection, though 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, then tested for glyceraldehyde-3-phosphate dehydrogenase (GADPH).^[2]

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 correlate 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.^[2]

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.^{[3][4][5]}

3. fMRIs of patients with schizophrenia

Numerous fMRIs, have reported disturbances in the fronto-temporal, fronto-cortical and cortical-cortical interactions. fMRI has been recently evaluated as more detailed and accurate over 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 reduction in volume, 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 compartment 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 the 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 neurodevelopmental disorder, that is manifested in its purest form, after the completion of development of the CNS. This correlates 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 heterogeneity among patients, the fact that there is a spectrum, rather than a single phenotype, justifies the term 'set of disorders'.^{[6][7]}

4. D5R and other neurotransmitters controlling plasticity

4.1. 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 on the D5R. DA and 5HT seem to have both synergistic and opposite effects, depending on the type of the region, they act upon. On the hippocampus, it is mentioned that 5HT plays a key role in memory and emotion regulation. Note that the hippocampus is divided in 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 5HT_{2A/2C}, which is strongly associated with schizophrenia. Also, the 5HT₇, the antagonism of which, has antidepressant properties, is also linked.^[8] 5HT_{2A} 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, 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 mechanism that is non-specific, when it comes to pro-cognitive effects.^[9]

4.2. Ach and D5R

Another neurotransmitter affected by the D5R is acetylcholine. D5R mediates the release of acetylcholine(Ach).^[10] Moreover knockout D5R mice appear to have a reduction in the Ach levels, in the same region. That clarifies the importance of the receptor.^[11] 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 of which, lies in the frequency of firing. The TAN are 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, in order 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 a prolonged use, the DA receptors have an 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.^[12] In any case, we see why the dysregulation of the D5R leads to DA-Ach imbalance, at least in the area of the striatum.

4.3. *GABA(A)R and D5R*

Another interaction of the D5R involves the GABA(A) receptor. This interaction takes place in the hippocampus, as evidence show. 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, so as 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.^[13]

4.4. *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.^[14] 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.

5. *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 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 correlate 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 where 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 in linked to the limbic system.^{[15][16]} 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.^[15]

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 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 take all three into consideration. The link is established through fronto-temporal pathway circuits, such as the fronto-striatal pathway.

6. 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 time 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, CA2 areas. As to the causes, the authors do not exclude a case of inflammation, as reported in the introduction section.^[17]

7. 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.^{[18][19]}

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 a further analysis needs to be performed.^[20] Given the prevalence of the 5HT2A/C in the hippocampus, we can assume that it is possibly linked to LTP, since evidence show that the 5HT2A is linked to LTP, associated with the prefrontal cortex and we may assume that the same goes for the latter^[21]. Since, the 5HT2 are the main mediators of DA release (Bortolozzi et al., 2005)^[22], 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, though the actions of the 5HT_{2A/C}.^[23] Taking that into account, we can assume that the hippocampus, that 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.^[24] This is due to the fact that postsynaptic 5HT_{2A}, and possibly 5HT_{2C} too, are mediated as to their effects, by other 5HT receptors.^[25]

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 GABA_A antagonists, which tend to increase LTP properties, mediated by glutamate. Glutamate is essential both for LTP and LTD. GABA_A agonists tend to decrease these cognitive processes, as shown by the use of benzodiazepines, which tend to affect memory, in higher concentrations.^[26] Given the association of GABA to the prefrontal cortex, the VTA and the NAc, we expect that the glutamate hypothesis, that 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.^[27] Also, the nAChRs participate in the plasticity process of the hippocampus too, as shown by the use of nicotine.^[28]

These dispersed information all lead to a general hypothesis. It seems that in schizophrenia, the 5HT_{2A/C} tend 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), in an effort 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. Moreover, 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.^[29] Despite that, evidence do not show an 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 in an effort to increase transmission.

Conclusion

The key components affecting the hippocampus are the nAChRs, the 5HT_{2A/C}, the D₅R, GABA(A) and NMDA receptors. Through this analysis, we explain how these systems support one another to bring about a stability to the hippocampus and other CNS regions, where the D₅R is involved, and due to the disease those regions tends to be dysregulated. There are some aspects of antipsychotics and other psychiatric medicine, 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 case of untreated psychosis however, the

hippocampus tends to dysfunction, due to the dysconnectivity with other parts of the CNS. To restore the hippocampus function, it is proposed to use antipsychotics that: 1) are $\alpha 4\beta 2$ & $\alpha 7$ nAChR agonists^[30] 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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