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

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There is no doubt that the dopamine D5 receptor has been unfairly neglected since its discovery and as a result we have no real knowledge base of its potential importance to neuropsychiatric disorders. As a consequence this review is both timely and important but given its title what is needed are good hypotheses of how the receptor subtype might contribute to the pathophysiology of schizophrenia. Is the dopamine hypothesis of schizophrenia so strong that any means of manipulating the dopamine system will be guaranteed to have a therapeutic impact. If ? if this is the author's opinion it needs to be substantiated by the key findings that support this view. There are gaps. For example and if anything the importance of this review is to remind those in the field that these questions demand answers phosphodiesterase PDE10 inhibitors have properties that indicate the ability to modulate dopaminergic neurotransmission yet they are clinically devoid of antipsychotic effects. Equally for this report we need a summary of the affinity of known antipsychotic compounds for D5 receptors in order to guage the possible impact t the receptor might exert on on their antipsychotic properties. The authors need to focus on the aspects of connectivity the disturbance of which is most likely to drive psychotic behaviour and so be able to generate hypotheses about why D5 is important. For example resting state connectivity between the frontal ecortex and the hippocampus is strengthened in the rat by exposure to ketamine which is counteracted by the atypical neuroleptic clozapine but not by the typical neuroleptic haloperidol Ishiwari et al (2014) neuropsychopharmacol 39:1635-1644 is clozapine capable of normalising resting state connectivity after ketamine does that explain its stronger antipsychotic properties? The mglu2/3 agonist has strong antipsychotic effects but only in in those carrying the 5-HT2A snp rs7330461 Liu et al 2012) Pharmacogenomics Journal (2012) 12:246-254. Pharmacogenomics journal how do the snp influence connectivity? With respect to BDNF the possibility is that D5ko mice might model negative symptoms is worthy of in snp depth investigation a decrease in expression of BDNF Assareh et al (2012 Pharmacol Biochem Behav 1003) 506-512. is related to the induction of depressive symptoms in man Demoreira et al., (2009) Best Practice and Research in clinical endocrinology and metabolism 23*1*) (1) 133-1441 just as an increase in its expression is related to antidepressant effects Sewell et al (2021) regul toxicol. pharmacol 125:1005002. The review by Khahn et al (2000) Neuroscience 100:689-699. Provides a useful summary of D5 distribution in mouse rat and human brain. Other useful insights maybe found in Broyd et al., (2009) neurosci & biobehav reviews 33:279-296. and Dresler et al., Biol Psychyatry 77:(2)177-186 (2015).

Overall this review lacks a thorough assessment of changes in connectivity in schizophrenia and any insights to what such approaches might aid treatment development The authors need to seriously consider whether progress in the field

warrents a review at this stage particularly in the absence of specific D5 selective pharmacological tools. I do believe we have much to learn from functional connectivity analysis but whilst it is important to draw attention to the D5 receptor as the paper stands a review seems somewhat premature and inappropriate. One final point, the high affinity of D5 for dopamine could indicate an autoreceptor arole i.e. rcontrolling opamine release, perhaps the D5ko mice would be useful to test this hypothesis as would be the determination of BDNF expression. Is the d5D5F173L mutation associated with any neuropsyciatric disorder? More information on this would be useful. Sobell et al., (1995) human molecular genetics 4(4)507-514. Find no association with disease.