Aetiology of bipolar disorder: contribution of the L-type voltage-gated calcium channels

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LTCCS ARE IMPLICATED IN THE PATHOLOGY OF BIPOLAR DISORDER

Bipolar disorder (BPD) is a common mental illness with significant morbidity and mortality.[1] Although evidence have suggested changes in oxidative stress, dopamine and inflammation in BPD, it is hard to define the aetiological mechanism of BPD clearly. Recently, some but not all candidate gene association studies, family-based association studies, linkage studies, genome-wide association studies (GWASs) and meta-analyses showed that mutation of L-type voltage-gated calcium channels (LTCCs) gene *CACNA1C* is implicated in the mechanism of BPD.[2–8] These findings support the possibility that BPD might have calcium channelopathy.[9]

LTCCs, which consist of a complex of alpha-1, alpha-2/delta and beta subunits in a 1:1:1 ratio, mediate the influx of calcium ions (Ca^{2+}) into the cell on membrane polarization. The alpha-1 subunit consists of 24 transmembrane segments and forms the pore through which ions pass into the cell. Cav1.2 is crucial in modulating kinetics of the LTCCs.[10] Cav1.2 is widely expressed in the heart[11 12] and brain.[13] So far, it is well known for its function in the heart.[11 12] LTCCs are located at both presynaptic nerve terminals and postsynaptic dendrites and dendritic spines. It initiates many physiological responses, including secretion, muscle contraction and gene transcription.

LTCCs have prominent roles in learning and memory processes, which might be related with the pathology of BPD.[14] LTCCs might control gene expression through coupling membrane depolarisation with cAMP response element-binding protein (CREB) phosphorylation via local Ca^{2+}/calmodulin-dependent protein kinase II (CaMKII) signalling.[15] This pathway and particularly CREB and BDNF are thought to be essential for learning and memory processes. Cav1.2 knockdown models have shown reduced CREB transcription and hippocampal LTP[16] implicating the importance of these channels in learning and memory process.

LTCCs appear to be particularly important for the normal function of dopaminergic[17] and 5-serotonergic[18] neuron function in the frontal cortex and mesolimbic dopamine systems, which contribute to the aetiology of BPD and might be correlated with LTCCs function. Because homozygous deletion of *CACNA1C* is lethal, the heterozygous *CACNA1C* knockout (HET) mouse was used for sleeping disorder[19] and mood-related behaviour studies.[20] *CACNA1C* heterozygous haploinsufficient mice manifested an attenuated response to the specific dopamine uptake inhibitor GBR12909, indicating that LTCCs critically regulated dopaminergic terminal function.[17]

The efficacy of the LTCCs blocker verapamil might alleviate acute mania in BPD,[21] while several others report no antimanic effects when verapamil was administered as a monotherapy.[22 23] It is reported that when verapamil was administered in combination with the mood stabiliser lithium to patients who were unresponsive to lithium,[24] there was significant improvement in manic symptoms.

Interestingly, the current research has showed LTCCs might be associated with the treatment response to the effect of antipsychotics in schizophrenia. Yu and colleagues[25] examined treatment response on LTCCs in patients with schizophrenia. They examined 2413 patients, together with a validation cohort of 1379 patients, and found that the rs2239063 in *CACNA1C* was associated with treatment response to olanzapine. Actually, psychiatrists often see patients with a mixture of manic and schizophrenic symptoms. Sometimes it is difficult to determine whether a patient has schizophrenia or BPD. We speculated that the same spectrum of genes might contribute to the causes of both BPD and schizophrenia.

CONTRADICTORY EVIDENCE FOR THE RELATIONSHIP BETWEEN LTCCS AND BIPOLAR DISORDER

Although many reports showed the association between *CACNA1C* and BPD,[2–8] the SNP was not well replicated among the published GWASs. Khalid and colleagues'[26] research showed that rs1006737 in *CACNA1C* has emerged as the most highly replicable SNP significantly associated with BPD. In their study, a total of 120 BPD and 120 control individuals from Pakistan were examined.[26] Kim and colleagues'[27] research showed that two other *CACNA1C* SNPs, namely *rs723672* and *rs1051375*, were associated with BPD while examining 287 Korean patients and 340 healthy controls.

CONCLUSIONS

Although accumulated reports showed the association between *CACNA1C* and BPD, the result was not well replicated among the public GWASs. The mechanisms of how genetic alterations in LTCCs affect the risk for BPD remain unknown. According to the current published

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research, LTCCs might be related with the monoaminergic signal pathway via the frontal cortex and mesolimbic systems. The brain-region-specific influence of *CACNA1C* risk SNPs on mania symptoms should be addressed. Neuroimaging, including MRI and fMRI studies, would be excellent methods to examine the brain-region-specific morphology and function in vivo. Future research should also focus on molecular neural circuit studies in animal models or in vitro studies about LTCCs function, especially neuroinflammation and neurotrophy function, which contribute critically to the aetiology of BPD. Second, based on the previous neurobiological results, we need to find more evidence of LTCCs for the differential diagnosis of major psychiatric disease as well. We might also identify biological pathways underlying specific shared or unique symptoms for the major psychiatric disease. Finally, more randomised placebo-controlled clinical studies should be carried out to confirm the clinical effect of calcium channel-targeted medicine (eg, LTCCs blocker) on BPD. Molecular mechanism of mood stabilisers targeted to calcium channels, especially LTCCs blocker, might also be well addressed in the future. We are looking forward for the further understanding of the LTCCs which may provide a breakthrough for the aetiological and pathogenetic research of BPD. Hopefully scientists and pharmacological companies will work together to develop more potentially safe and effective new drugs based on LTCCs in the future.

Correction notice This article has been corrected since it was first published. This article was not published under an Open Access licence. This has now been corrected.

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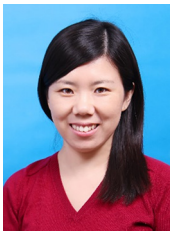

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