IL-6R, JAK1 AND JAK2 ARE PREDICTED TO BE TARGETS UNDERLYING THE ANTIDEPRESSANT AND ANTISUICIDAL PROPERTIES OF KETAMINE

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Major depressive disorder (MDD) and suicidal behavior are complex psychiatric conditions with a multifactorial etiology that involves neuroinflamation, neurodegeneration, redox system imbalance, and alterations in neurotransmission and neuroplasticity mechanisms. Ketamine has been shown to be effective for the treatment of refractory MDD, and in suicide prevention. The most investigated mechanism of action of ketamine is related to the NMDA receptor antagonism. However, ketamine may have multiple pharmacological targets responsible for its antidepressant and antisuicidal properties. Therefore, this study aimed to predict new targets of ketamine enantiomers related to their antidepressant and antisuicidal effects. The list of target genes associated with depression and suicidal behavior were obtained from DisGeNET database using the keywords "Major Depressive Disorder; CUI: C1269683" and "completed suicide; CUI: C0852733". The protein-protein network was constructed using STRING and the statistical analysis of the network and the final layout were performed in Cytoscape. Molecular docking were performed in Dockthor and molecular interactions were analised in Ligplot+. Therefore, bioinformatics integrated analysis provided an overview of the main targets predicted as implicated in the antidepressant and antisuicidal properties of ketamine. As main results, IL-6 is a central node in MDD and suicide in network pharmacology analysis. After filtering the nodes with Cytoscape's diffusion algorithm, we performed molecular docking and both ketamine enantiomers may interact with JAK1, JAK2 and IL-6R. This result suggests the potential role of the IL-6/JAK/STAT3 pathway in the antidepressant and antisuicidal effects of ketamine enantiomers.