M48. TRANSCRIPTOMIC SIGNATURES OF SCHIZOPHRENIA REVEALED BY DOPAMINE PERTURBATION OF LYMPHOBLASTOID CELL LINES

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Background The dopaminergic hypothesis of schizophrenia postulates a dopamine D2 receptor (DRD2)-mediated hyperdopaminergic neurotransmission in schizophrenia. However, dopamine is also known to have other, non-receptor-mediated effects, including oxidative mechanisms leading to apoptosis. While oxidative processes have been reported to contribute to dopamine neuron loss in Parkinson's disease, their role in schizophrenia remains little studied.

Methods We performed a dopamine perturbation on lymphoblastoid cell lines from 515 schizophrenia cases and 692 controls, and studied the resultant RNAseq profiles.

Results We found that dopamine had widespread effects on expression profiles, though these effects were likely not mediated through dopamine receptors. Upon stimulation, of the reliably expressed genes, 3,756 (19%) had expression changes of >1 standard deviation at a false discovery rate <5%. Of those genes, 539 showed differential response in schizophrenia cases and controls. Pathway analyses uncovered that the set of differentially expressed genes were enriched for two factors: (1) brain expression, and (2) immune and/or apoptotic mechanism involvement. The latter observation is consistent with schizophrenia genome-wide association study findings where the most significant locus is the extended major histocompatibility complex region, which contains numerous genes with fundamental roles in immune response.

Discussion Our findings suggest that dopamine may play a role in schizophrenia pathogenesis through modulating immune response and apoptosis. Our results also suggest the utility of pathophysiologically relevant perturbation experiments in appropriate cells to investigate the biology of complex mental disorders.

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