MAOA and mechanisms of panic disorder revisited: from bench to molecular psychotherapy

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Panic disorder with agoraphobia (PD/AG) is a prevalent mental disorder featuring a substantial complex genetic component. At present, only a few established risk genes exist. Among these, the gene encoding monoamine oxidase A (MAOA) is noteworthy given that genetic variation has been demonstrated to influence gene expression and monoamine levels. Long alleles of the MAOA-uVNTR promoter polymorphism are associated with PD/AG and correspond with increased enzyme activity. Here, we have thus investigated the impact of MAOA-uVNTR on therapy response, behavioral avoidance and brain activity in fear conditioning in a large controlled and randomized multicenter study on cognitive behavioral therapy (CBT) in PD/AG. The study consisted of 369 PD/AG patients, and genetic information was available for 283 patients. Carriers of the risk allele had significantly worse outcome as measured by the Hamilton Anxiety scale (46% responders vs 67%, P=0.017). This was accompanied by elevated heart rate and increased fear during an anxiety-provoking situation, that is, the behavioral avoidance task. All but one panic attack that happened during this task occurred in risk allele carriers and, furthermore, risk allele carriers did not habituate to the situation during repetitive exposure. Finally, functional neuroimaging during a classical fear conditioning paradigm evidenced that the protective allele is associated with increased activation of the anterior cingulate cortex upon presentation of the CS+ during acquisition of fear. Further differentiation between high- and low-risk subjects after treatment was observed in the inferior parietal lobes, suggesting differential brain activation patterns upon CBT. Taken together, we established that a genetic risk factor for PD/AG is associated with worse response to CBT and identify potential underlying neural mechanisms. These findings might govern how psychotherapy can include genetic information to tailor individualized treatment approaches.
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