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Polymorphisms in Genes Modulating the Dopamine System: Do They Influence Outcome and Response to Medication After Traumatic Brain Injury?

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Introduction

In clinical practice it is common to see different functional outcomes in individuals with similar degrees of traumatic brain injury (TBI) and comparable pre-injury intellectual, educational, and functional capabilities. Similarly, individual responses to medications can vary enormously. These differences suggest that environmental and other host factors play important roles in outcome. Host genotype might be one such factor. Our knowledge of the role of genetic factors in response to trauma and recovery from trauma, including reactivity to drugs, is in its infancy. However some important preliminary findings are emerging.(for example see 1, 2) This article focuses on candidate polymorphic alleles in genes modulating central dopaminergic function to illustrate some of the underlying principles and prospects for the future.

An array of genetic responses is triggered by neurotrauma both acutely and over time. (3, 4) Polymorphisms in genes responding to neurotrauma, and genes modulating cognition-associated neurotransmitter systems may influence the acute response to trauma as well as adaptation to injury-induced constraints and response to medications used to promote recovery. Polymorphisms that under normal conditions confer no advantage or disadvantage to the host, may, under conditions of injury or decreased reserve, come to play important roles as mediators of outcome.

As a starting point, it is useful to consider four broad categories in which genes could play an important role in outcome after trauma: these include modulation of 1) injury extent, 2) recovery from injury, 3) pre-injury cognitive capacities and reserve, and 4) response to treatment. Each of these four broad categories involves multiple processes and thus is under complex polygenic control. An important characteristic of polygenic traits is that the effect of individual alleles might be subtle but may be additive or interactive with other alleles. Additional power to detect genetic influences on outcome measures can be gained, therefore, by considering an ensemble of candidate alleles that may interact together to produce the trait (e.g. memory impairment or “poor recovery”) (see 5 for full discussion).(5) Many of the genes participating in these four broad domains have not been identified, much less sequenced nor functional polymorphic alleles identified. However, important nodal points in each of these major phases have been defined and several tantalizing candidate genes with interesting functional polymorphisms have been discovered.

Dopamine System Genes

The central dopaminergic system plays a critical role in motor function (the nigro-striatal pathway), hormonal stasis (the tubero-infundibular pathway), motivated behavior, mood homeostasis and reward circuitry (the meso-limbic pathway), and cognition (meso-cortical pathway). Dopaminergic and other catecholaminergic systems are vulnerable to injury and dysregulation associated with TBI.(see 6, 7 for discussion) The dopaminergic system may also play a role in neural plasticity and repair through effects on brain derived neurotrophic factor (8), in recovery of motor function after stroke and TBI (as seen in animal models and some human studies) (see 9 for review), and in cognitive reserve and treatment of cognitive deficits after TBI.(10) Thus, polymorphisms in genes involved in the dopaminergic system have the potential to influence a wide array of critical human functions. Candidate genes include those coding for dopamine receptor sub-types, dopamine re-uptake (the dopamine transporter or DAT), and dopamine metabolism (catechol-o-methyl transferase or COMT).

Dopamine D2 Receptor (DRD2)

The DRD2 gene is located on chromosome 11q23 and has several polymorphisms with fairly high minor allele frequencies. Another polymorphism, TAQ1 A (henceforth referred to as rs1800497), located in the adjacent gene ANKK1, may also regulate the expression of D2 receptors. It has been the focus of significant study (11) in a variety of neuropsychiatric disorders including TBI. rs1800497 is a C/T single nucleotide polymorphism (SNP). The T allele has been associated with a 40% reduction in the expression of D2 receptors in the striatum and perhaps other cortical regions, without change in receptor affinity (12, 13). Rs1800497 was originally regarded as a DRD2 polymorphism, and the discovery of its location elsewhere is somewhat surprising, raising the question whether this SNP is actually responsible for the observed associations in neuropsychiatric disorders. An alternate explanation is that it is strongly linked to another allele of an as yet undiscovered functional SNP located on the DRD2 gene. In other words, every person with an rs1800497 T allele also has this undiscovered allele. Since we do not know of the existence of this allele, we end up erroneously attributing causality to the rs1800497 T allele. Alternatively rs1800497 may regulate the expression of DRD2 levels in some unclear fashion (14). Our group found that the T allele of rs1800497 was associated with poorer performance on a measure of episodic memory (the California Verbal Learning Test - recognition trial). There also was a significant diagnosis-by-allele interaction on measures of response latency (Gordon Continuous Performance Test reaction times) whereby subjects with TBI and the T allele had the worst performance (15).

Catechol-o-methyl transferase (COMT)

COMT catalyzes the metabolic breakdown of catecholamines through the methylation of dopamine and norepinephrine. The gene for COMT is located on the long arm of chromosome 22. There is a common (~ 45% minor allele frequency) functional polymorphism of this gene characterized by a single nucleotide change from G to A at position 472. This results in a change of amino acids from valine to methionine (16). The valine version (val allele) is almost four times as active as the methionine version of the gene (met allele) at normal body temperature. Thus individuals homozygous for the val allele presumably metabolize DA much more rapidly than those with the met allele. This is of particular importance in the frontal cortex, where the dopamine transporter (DAT) shows relatively less expression compared to other brain regions (17) and thus COMT becomes a major modulator of dopaminergic tone in the frontal cortex.

Changes in COMT activity alter both frontal dopaminergic activity and cognitive capacity in both animals (18, 19) and humans (20-23). Several studies examining measures of frontal-

executive function in healthy subjects and those with a variety of neuropsychiatric disorders (e.g. 21, 22, 23) report that the val allele is associated with poorer performance (more perseveration errors) and that there is an allelic load effect (i.e., val/val homozygotes did worse than val/met heterozygotes). The met allele was associated with reduced (i.e., more “efficient”) regional brain activation while performing a working memory task (21, 24). Lipsky et al. (25) studied 113 individuals with TBI and found poorer performance on some measures of executive function in those with a val allele.

Other Potential Dopaminergic Candidate Genes and Alleles

Although there are numerous other polymorphisms in dopamine system genes, little is known about which ones are functional and even less about whether they play a role in outcome and function after TBI. A sampling of those with theoretical interest that are currently under study in our group is described below.

Dopamine D3 Receptor (DRD3)

The DRD3 is located on the long arm of chromosome 3. Although not yet studied in TBI, the Ser⁹Gly (Bali/MscI) (11) allele is of some theoretical interest. This mutation is located at the number 9 amino acid position and results in either serine (allele 1) or glycine (allele 2) at that position. Glycine confers an increased affinity for dopamine relative to the serine. The alteration in receptor affinity for dopamine makes this gene of theoretical interest.

Dopamine D4 Receptor (DRD4)

The DRD4 gene is located on the short arm of chromosome 11. There are numerous allelic variants, several of which have functional significance, although their role in specific neuropsychiatric disorders is not clearly defined. The most commonly studied gene region is the sequence that codes for the third cytoplasmic loop of the receptor. This section contains a variable number of 48 base pair repeats that show significant differences in DA-mediated coupling to adenylyl-cyclase (11, 26, 27). Several reports have shown an association between the D4.7 allele and ADHD and increased novelty seeking (11, 28) in adults, neonates (29), and D4 receptor knock-out mice (30).

Dopamine Transporter (DAT)

After release from synaptic vesicles into the synapse, DA binds to pre-synaptic membrane proteins known as transporters and is taken back into the pre-synaptic neuron. Blockade of DAT is thought to be the mechanism of action for many psychoactive drugs including cocaine, amphetamine, methylphenidate, and bupropion. The gene for DAT is located on the short arm of chromosome 5 and contains a 40 base-pair variable number of tandem repeats (VNTR), in the untranslated 3' region. These variations appear to have an effect on the expression of DAT (31) thus raising the theoretical possibility that polymorphisms in this gene might impact central dopaminergic tone as well as influence response to dopaminergic agonist agents used to treat cognitive deficits after TBI.

Conclusion

The study of the role of genetic variation in modulating outcome after TBI is at a very early stage. The effect of genetic variation on treatment outcome, including potential response to drugs, is even less advanced. However, it is encouraging that even with relatively small sample sizes, several groups have found genetic effects that influence cognitive outcome. These findings need replication before firm conclusions can be reached. In addition, the effect sizes in these studies are quite modest. Thus, additional host and environmental factors certainly contribute to outcome variance after seemingly similar degrees of injury.

The molecular processes underlying the brain's response to trauma are enormously complex. Better predictive results and individualized choice of cognition-enhancing medication may follow from approaches that look at the interaction of different polymorphisms within and across different relevant pathways and model the polygenic control of complex behaviors and outcome measures. This approach holds much promise and it will be facilitated by the dramatic advances in microarray technology that allow for genotyping across many different genetic loci at a reasonable cost.

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