General summary
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MILLENNIUM ARTICLE

The amygdala: vigilance and emotion
M Davis, PJ Whalen

Here the authors provide a review of the animal and human literature concerning the role of the amygdala in fear conditioning, considering its potential influence over autonomic and hormonal changes, motor behavior and attentional processes. A stimulus that predicts an aversive outcome will change neural transmission in the amygdala to produce the somatic, autonomic and endocrine signs of fear, as well as increased attention to that stimulus. It is now clear that the amygdala is also involved in learning about positively valenced stimuli as well as spatial and motor learning and this review strives to integrate this additional information. Review of available studies examining the human amygdala covers both lesion and electrical stimulation studies as well as the most recent functional neuroimaging studies. Where appropriate, the authors have attempted to integrate basic information on normal amygdala function with our current understanding of psychiatric disorders, including pathological anxiety.

IMMEDIATE COMMUNICATION

Association between novelty seeking and the −521C/T polymorphism in the promoter region of the DRD4 gene
Z Ronai, A Szekely, Z Nemoda, K Lakatos, J Gervai, M Staub, M Sasvari-Szekely

Possible association of the DRD4 VNTR and Novelty Seeking has been a controversial issue since the first two reports by Benjamin and Ebstein in 1996. A novel explanation of unsuccessful replications is raised by demonstrating significant effect of a single nucleotide polymorphism (−521C/T) in the regulatory region of the DRD4 gene on Novelty Seeking. Significant association was found between high Novelty Seeking score on the Temperament and Character Inventory (TCI) personality questionnaire and the CC genotype in a Hungarian sample of 109 healthy volunteers, being even more pronounced for female subjects only. This is the first replication of the findings of Okuyama et al published in Molecular Psychiatry this year, showing that the polymorphic regulatory region of the DRD4 gene might significantly influence Novelty Seeking not only in Japanese but also in a Caucasian sample.

ORIGINAL RESEARCH ARTICLES

Mutation screening of the Wolfram gene in psychiatric patients
R Torres, E Leroy, X Hu, A Katrivanou, P Gourzis, A Papachatzopoulou, A Athanassiadou, S Beratis, D Collier, MH Polymeropoulos

Patients with Wolfram’s syndrome (WS), a rare genetic disorder characterized by juvenile diabetes and optic atrophy, are prone to psychiatric disorders. Given the significance of mutations on the WS gene in patients with WS, the present experiment examined the contribution the WS gene may have in psychiatric disorders. Using sequence analysis, patients with psychiatric disorders (including schizophrenia, schizoaffective disorder, bipolar disorder and depression) were screened for mutations on the WS gene comparable to those found in patients presenting WS. Although 24 new variations were discovered, none of the psychiatric patients screened carried mutations typical of those seen in WS. The authors’ findings suggest that WS-specific mutations in the WS gene may not play a significant role in the etiology of psychiatric disorders.

Protein kinase A and Rap1 levels in platelets of untreated patients with major depression
J Perez, D Tardito, G Racagni, E Smeraldi, R Zanardi

The last decade brought about a shift in the theoretical framework regarding affective disorders. During this period, several investigations have shown dysfunctions of the cAMP signaling pathway in patients with affective disorders. Within this context, the authors have recently found that the levels of the protein kinase A, a key element of this pathway, and those of Rap1, a protein kinase A substrate, are altered in bipolar patients. Thus, the current study was designed to assess the levels of these proteins in platelets of unipolar patients. The emerging picture is that depressed but euthymic unipolar patients have altered levels of protein kinase A and Rap1. However, these abnormalities are somewhat different from those observed in bipolar patients, thus suggesting that affective disorders may be associated to distinctive biochemical abnormalities of a common pathway. These findings support the role of cAMP signaling in the molecular pathways underlying affective disorders.
Single nucleotide polymorphisms distinguish multiple dopamine transporter alleles in primates: implications for association with attention deficit hyperactivity disorder and other neuropsychiatric disorders

GM Miller, R De La Garza II, MA Novak, BK Madras

The human dopamine transporter is a brain protein that regulates levels of the chemical message dopamine. The gene encoding this transporter contains a repeated sequence of variable length in the human population. A dopamine transporter gene with a 10-copy repeat reportedly is associated with a small proportion of symptom variance in attention deficit hyperactivity disorder. As the comparable repeat sequence is not found in rodents, the authors hypothesized that this report sequence may exist in another primate species, rhesus monkeys. The monkey transporter gene, investigated in 22 monkeys that displayed various levels of activity, contained a repeat sequence similar to human. The sequence length was fixed but the authors detected several single ‘letter’ differences between animals, one of which was suggestive, but not predictive, of hyperactive behavior. The human dopamine transporter gene also varied in sequence. Thus, there is a diversity of genetic sequences between individuals that may be more extensive and significant to dopamine-related disorders than differences in the length of this region. Accordingly, the authors propose that the search for genetic involvement in dopamine transporter-related disorders should be expanded from investigation of length to investigation of sequence.

No association or linkage between polymorphisms in the genes encoding cholecystokinin and the cholecystokinin B receptor and panic disorder

SP Hamilton, SL Slager, L Helleby, GA Heiman, DF Klein, SE Hodge, MM Weissman, AJ Fyer, JA Knowles

Panic disorder is a common disorder of unknown etiology. Injection of the cholecystokinin induces anxiety behaviors and panic attacks in studies of animals and humans. Recent genetic studies that compared groups of individuals with or without panic disorder have suggested that polymorphisms in the genes for cholecystokinin (CCK) and one of its receptors, the cholecystokinin B receptor (CCKBR), may be associated with panic disorder. In the present study, a large collection of panic disorder trios and multigenerational pedigrees was examined, and no association or linkage was found between the polymorphism in the promoter of the CCK gene and panic disorder. Similarly, a dinucleotide repeat in the CCKBR gene was neither associated nor linked with panic disorder. These findings offer no support for involvement of these genes in panic disorder, and stress the importance of family-based methods in candidate gene studies.

Evidence that activities of erythrocyte free radical scavenging enzymes and the products of lipid peroxidation are increased in different forms of schizophrenia

H Herken, E Uz, H Özyurt, S Söğüt, O Virit, Ö Akyol

Antioxidant status may be changed in schizophrenia and thus may induce lipid peroxidation, thereby affecting the pathophysiological of this disorder. Oxidative stress in subtypes of schizophrenia was examined. Antioxidant status and lipid peroxidation in schizophrenia patients (disorganized (n = 21), paranoid (n = 26) and residual types (n = 18)) was determined by assaying free radical scavenging enzymes, superoxide dismutase (SOD), glutathione peroxidase (GSH-Px) and catalase (CAT), and the level of thiobarbituric acid reactive substances (TBARS) in red blood cells. The authors found a significant increase in SOD activity in the residual group compared to the paranoid group. CAT activity was also increased in disorganized, paranoid, and residual groups compared to the control group. GSH-Px activity was markedly increased in the study groups except the paranoid group. Statistically significant increases in TBARS levels of red blood cells were found in all of the study groups. These findings suggest that changes in the antioxidant status and lipid peroxidation in red blood cells may be correlated in schizophrenia subtypes.

Lack of evidence to support the association of the human prion gene with schizophrenia

M-T Tsai, Y-C Su, Y-H Chen, C-H Chen

Human prion disease is a progressive neurodegenerative disease characterized by the spongiform pathology in the brain. In addition to neurological symptoms, psychiatric manifestations are common in some patients. Recently, a novel missense mutation with asparagine-to-serine substitution at codon 171 of the human prion gene (N171S) was identified in a family with severe psychiatric symptoms. This finding suggests that the prion gene may be a susceptibility gene for psychiatric disorders. Hence, the authors searched the human prion gene mutations in Chinese schizophrenic patients from Taiwan. Two polymorphisms were identified, a methionine/valine at codon 129 (M129V) and a glutamate/lysine at codon 219 (E219K), respectively. However, no further mutations were identified. Case-control association study of these two polymorphisms did not reveal association with schizophrenia. Hence, the authors’ results suggest that the prion gene may not play a major role in conferring susceptibility to schizophrenia.

Association between –G308A tumor necrosis factor alpha gene polymorphism and schizophrenia

R Boin, R Zanardini, R Pioli, CA Altamura, M Maes, M Gennarelli

Dysregulation of the immune system has been linked to the pathophysiology of schizophrenia. Evidence of
immune activation has been derived from studies that detected abnormal levels of proinflammatory cytokines in peripheral blood and cerebrospinal fluid from schizophrenic patients. Cytokines are involved in normal CNS development as well as in the pathogenesis of many neuropsychiatric disorders, acting directly on neural cells or modulating neurotransmitter and neuropeptide systems. In particular TNFα can exert neurotrophic and neurotoxic effects, influencing neural cell growth and proliferation. TNFα gene lies in a locus on the small arm of chromosome 6 recently associated with genetic susceptibility to schizophrenia. The authors studied the distribution of G308A TNFα gene polymorphism in schizophrenic patients and found that frequency of the TNF2(A) allele is significantly increased in the patient group. Also genotype distribution is significantly different. These data suggest a potential role of TNFα as a candidate gene for susceptibility to schizophrenia and suggest that immune dysregulation in schizophrenic patients could also have a genetic component.

A novel polymorphism of the brain-derived neurotrophic factor (BDNF) gene associated with late-onset Alzheimer’s disease

H Kunugi, A Ueki, M Otsuka, K Isse, H Hirasawa, N Kato, T Nabika, S Kobayushi, S Nanko

Several lines of evidence have suggested altered functions of brain-derived neurotrophic factor (BDNF) in the pathogenesis of neurodegenerative diseases including Alzheimer’s disease (AD). In their search for polymorphisms in the 5’-flanking and 5’-noncoding regions of the BDNF gene, the authors found a novel nucleotide substitution (C270T) in the noncoding region. They performed an association analysis between this polymorphism and AD in a Japanese sample of 170 patients with sporadic AD (51 early-onset and 119 late-onset) and 498 controls. The frequency of individuals who carried the mutated type (T270) was found to be significantly increased in patients with late-onset AD than in controls (P = 0.00004, odds ratio: 3.8, 95% CI 1.9–7.4). However, there was no significant difference in the genotype distribution between the patients with early-onset AD and controls. These results suggest that the C270T polymorphism of the BDNF gene or other as yet unknown polymorphisms, which are in linkage disequilibrium may increase susceptibility to late-onset AD.

Human homolog of the mouse imprinted gene
Impact resides at pericentric region of chromosome 18 within the critical region for bipolar affective disorder

K Kosaki, T Suzuki, R Kosaki, H Yoshihashi, M Itoh, Y Goto, N Matsuo

A limited number of genes (so-called imprinted genes) in the human genome are preferentially expressed from either the paternally derived or the maternally derived allele. Several mapping studies of families with multiple individuals who have bipolar affective disorder (BPAD) have demonstrated that the trait may be linked to the pericentric region of chromosome 18 (18cen) and that in some 18cen-linked families a parent-of-origin effect is observed in the transmission of the BPAD trait. Thus, it is possible that the putative BPAD susceptibility gene may be imprinted. The authors cloned IMPACT, the human homolog of the mouse imprinted gene Impact and mapped it to 18cen within the critical interval for BPAD. Since very limited numbers of genes in the entire genome are imprinted, IMPACT represents a candidate gene for BPAD susceptibility. Alternatively, other as yet unknown imprinted gene(s) adjacent to IMPACT could contribute to the BPAD trait, since multiple imprinted genes may occasionally form clusters.

Exclusion of the Darier’s disease gene, ATP2A2, as a common susceptibility gene for bipolar disorder

NJO Jacobsen, EKE Franks, G Elvidge, I Jones, P McCandless, MC O’Donovan, MJ Owen, NJ Craddock

The authors have previously described the cosegregation of Darier’s disease, an autosomal dominant skin disorder, and bipolar affective disorder (manic depression). The gene for Darier’s disease was mapped by several independent groups to chromosome 12q23–q24.1 and identified as ATP2A2. The authors along with other groups have found evidence to suggest the presence of a susceptibility locus for bipolar disorder on chromosome 12q. The ATP2A2 gene is involved in the regulation of intracellular calcium concentration, important in correct neuronal functioning. In this study the authors have analyzed the ATP2A2 gene for mutations in order to ascertain whether it plays a role in determining susceptibility to bipolar disorder. The authors conclude that this gene is unlikely to determine disease susceptibility in their patient sample.

TPH and suicidal behavior: a study in suicide completers

G Turecki, Z Zhu, J Tzenova, A Lesage, M Séguin, M Tousignant, N Chawky, C Vanier, O Lipp, M Alda, R Joober, C Benkelfat, GA Rouleau

Over the last years, several lines of investigation have been suggesting that suicide is not just a drastic response to extreme stress. Indeed, studies have been indicating that factors from our biological constitution may make us more or less predisposed to this tragic event. Among these biological factors are genes. Several studies investigating subjects who attempted, but who did not complete suicide, suggested that one specific gene, known as the tryptophan hydroxylase gene, or TPH, may be among the genes that confer some degree of predisposition to suicidal behavior. This study confirmed this evidence by investigating a sample of individuals who died by suicide. A better understanding of the factors that are involved in the predisposition to suicide will eventually help us deal with
one of the most difficult challenges currently facing the mental health professional, namely suicide prevention.

**Differential expression of diacylglycerol kinase iota and ribosomal protein L18A mRNAs in the brains of alcohol-prefering AA and alcohol-avoiding ANA rats**

*W Sommer, C Arlinde, L Caberlotto, A Thorsell, P Hyytia, M Heilig*

The neurobiology of alcohol self-administration has been widely studied, but the molecular determinants of this complex behavior remain largely unidentified. Here, the authors analyzed global expression profiles from cerebral cortex of alcohol preferring and non-prefering rat strains, to screen for differences in mRNA expression. Covering roughly 10% of the expressed genes, the authors identified two transcripts which co-segregated in with the alcohol preferring phenotype. In the alcohol preferring line, a strongly reduced expression was found of ribosomal protein L18A, a constituent of the large subunit of the cytoplasmic ribosomes but also a potential regulator of several inducible transcription factors. In contrast, these rats show increased expression of diacylglycerol kinase iota, a member of a larger enzyme family generating phosphatic acid from diacylglycerol, which in turn is a key activator of protein kinase C. The present approach produces correlative results which cannot be directly linked to function, but may direct research into new areas such as the identification of second messenger pathways involved in the development of dependence. This may in turn direct efforts to develop novel pharmacological treatments for alcohol dependence.

**Association study of the low-activity allele of catechol-O-methyltransferase and alcoholism using a family-based approach**

*T Wang, P Franke, H Neidt, S Cichon, M Knapp, D Lichtermann, W Maier, P Propping, MM Nöthen*

Catechol-O-methyltransferase (COMT) is a major component of the metabolic pathways of neurotransmitters such as dopamine, adrenaline, and noradrenaline. The activity of COMT is known to vary within the population; it exists in common high- and low-activity forms. Recently, the low-activity form was reported to contribute to the development of late-onset alcoholism in men. The present study extends this previous investigation by utilizing a family-based association approach, and by including individuals with early-onset alcoholism. Although no significant result was found in the overall sample of 70 nuclear families, each consisting of parents and an affected offspring, the authors observed a preferential transmission of the low-activity allele to patients with an early onset of disease (*n* = 32, TDT = 4.83, *P* = 0.028). The authors’ results provide further evidence for an involvement of the COMT low-activity allele in the development of alcoholism and demonstrate the need for further studies in large samples of alcoholic patients.

**Progesterone modulation of D5 receptor expression in hypothalamic ANF neurons: the role of estrogen**

*D Lee, L Wang, P Dong, T Tran, D Copolov, AT Lim*

Estrogen may play a protective role in schizophrenia. In women, the onset of the illness occurs far later than it does in men and there is a peak incidence of the illness after menopause. Moreover, estrogen supplements given together with antipsychotic drugs also improve clinical outcomes. The authors have previously shown that estrogen augmented the expression of dopamine D5 receptors in central neurons and suggested that this effect may contribute, in part, to the protective role of the steroid. This is consistent with recent reports that negative symptoms in schizophrenia may involve a diminution of D5 and D1 receptors in the prefrontal cortex. In the present studies, the authors have further examined the role of another important ovarian steroid, progesterone and showed that whereas by itself progesterone produced little effect, the steroid enhanced the augmenting effect of estrogen on D5 receptor expression. The findings suggest that progesterone and estrogen may be given together with antipsychotic drugs to further enhance therapeutic efficacy in patient management.

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**Editor**