Molecular Psychiatry (2000) 5, 4–7

www.nature.com/mp

General summary

J Vianello and J Licinio

NIMH, Bethesda, MD, USA

PERSPECTIVE

The role of stress in the pathophysiology of the dopaminergic system

L Pani, A Porcella, GL Gessa

In recent decades, the term 'stress' has changed its meaning from that of a 'simple' emergency system (the so called 'fight or flight' response); it is now seen more as a constant apparatus for monitoring internal and external stimuli, using changes in environmental conditions as a means of regulating the organism. Research shows that the dopaminergic system is important not only in terms of pleasurable feelings or for reward learning, but also as it allows the organism to react to external factors, thus allowing it to cope with the external world. Such a system is vital not only for the performance of routine checking, but also to decide upon priorities in order to maintain vital functions, such as drinking, eating and reproduction. The failure of these functions characterizes a number of stress-related neurological and psychiatric disorders.

MILLENNIUM ARTICLE

Psychiatric genetics: back to the future

MJ Owen, AG Cardno, MC O'Donovan

For the last decade or more geneticists have been predicting that advances in molecular genetics are going to revolutionise our understanding of psychiatric disorders and human behaviour. However, with a few exceptions, these expectations have yet to be fulfilled. As the century draws to a close and we contemplate the prospect of the complete sequence of the human genome, we consider the state of the field, how it might advance, the problems to be faced and the resources required. Despite the undoubted complexities of psychiatric genetic research, significant advances have been made, most notably in the field of Alzheimer's disease. The prospects for determining the genetic basis of other common psychiatric disorders are good, but important difficulties still have to be overcome. Technical and methodological advances are certainly required. However, ultimately the identification of genetic risk factors for mental disorders and the translation of this into improved patient care will depend as much upon the traditional medical disciplines of clinical description and epidemiology and our ability to combine these with genetic, psychological and sociological approaches.

IMMEDIATE COMMUNICATION

The human serotonin transporter gene linked polymorphism (5-HTTLPR) shows ten novel allelic variants

M Nakamura, S Ueno, A Sano, H Tanabe

Transcription of the serotonin transporter (5-HTT) gene is modulated by a common polymorphism in its upstream regulatory region (5-HTT gene-linked polymorphic region: 5-HTTLPR). The 5-HTTLPR consists of variation of the repetitive sequence. A deletion/insertion in the 5-HTTLPR was first reported to create a short (S) allele and a long (L) allele (14- and 16-repeats, respectively). The present study examined the 5-HTTLPR polymorphism in detail and identified novel sequence variants, concluding that the alleles reported as S and L are divided into four and six types of allelic variant, respectively. The total number of alleles in the 5-HTTLPR was 14. In addition, a significant ethnic difference between Japanese and Caucasian populations was observed for distributions of alleles and genotypes. These results suggest that the analyses of the 5-HTTLPR should be revised by genotyping with a more complete subdivision of alleles.

ORIGINAL RESEARCH ARTICLES

Dopamine induces a biphasic modulation of hypothalamic ANF neurons: a ligand concentration-dependent effect involving D_5 and D_2 receptor interaction

D Lee, W Huang, AT Lim

Dopamine, an important chemical signal or neurotransmitter of the brain, is closely involved in drug abuse, cognitive abnormalities and psychotic illnesses. The biological actions of dopamine underlying these conditions however, are complex and remain unclear. This is because the neurotransmitter may activate or inhibit the functions of brain cells, depending on the types of dopamine acting sites or receptors present. Therefore, various receptors may work in conjunction with or in opposition to one another on the same neurons, and aberrant interactions of the receptors have been implicated in functional disorders of the brain. By growing a group of well-defined brain cells in petri dishes, which respond to dopamine, the authors have now identified and characterized two important subgroups of dopamine receptors, namely, D_5 and D_2 receptors. The receptors interact to produce a novel effect culminating in the dual actions described above, depending on the availability of dopamine. These

interesting findings have provided an insight into the neurobiological effects that may be related to the therapeutic efficacy of antipsychotic drugs. It may therefore open up new ground for the development of the drugs with better clinical effectiveness.

Identification and analysis of new sequence variants in the human tryptophan hydroxylase (TpH) gene
A Paoloni-Giacobino, D Mouthon, C Lambercy, M Vessaz, S Coutant-Zimmerli, W Rudolph, A Malafosse, C Buresi

Tryptophan hydroxylase (TpH) gene, coding for the rate-limiting enzyme of serotonin synthesis, is certainly a good candidate in psychiatric diseases. In this study, the authors identified six new variants and analyzed five previously described polymorphisms (four in the promoter region and one in intron 7). Identification of these new polymorphisms and particularly of a microsatellite in the 3′ region of the gene allowed them to construct haplotypes that can be a good tool in association studies between the TpH gene and psychiatric disorders. Not only will analyses of these new sequence variants facilitate new population and family-based association studies, but they will also help to resolve discrepancies between previous studies which attempted to associate a variant in intron 7 of TpH gene with manic depressive illness, depression, impulsivity and/or aggression.

A haplotype at the DBH locus, associated with low plasma dopamine β-hydroxylase activity, also associates with cocaine-induced paranoia
JF Cubells, HR Kranzler, E McCance-Katz, GM Anderson, RT Malison, LH Price, J Gelernter

Low plasma levels of dopamine β-hydroxylase (DβH) are associated with vulnerability to psychotic symptoms. Plasma DβH level is a heritable trait, controlled predominantly by DBH, the structural gene encoding DβH protein. Cubells and colleagues hypothesized that molecular variants at DBH, that associate with lower levels of plasma DβH protein, would also associate with greater vulnerability to cocaine-induced paranoia. After identifying a haplotype at DBH that associates with low plasma DβH levels, they found the haplotype more frequently in European-American cocaine users who endorsed cocaine-induced paranoia, than in those who denied cocaine-induced paranoia. The association reflects a striking under-representation of the low-DβH-associated DBH haplotype in cocaine users who deny cocaine-induced paranoia. Thus, variation at DBH that influences DβH biochemical phenotype may also alter vulnerability to cocaine-induced paranoia.

Identification of a polymorphism in the promoter region of DRD4 associated with the human novelty seeking personality trait
Y Okuyama, H Ishiguro, M Nankai, H Shibuya, A Watanabe, T Arinami

An association between dopamine D4 receptor gene (DRD4) exon III polymorphism and Novelty Seeking personality has been controversial. The authors searched for polymorphisms in the 5′ region of DRD4 and explored relationships between polymorphisms identified and personality traits measured by the Temperament and Character Inventory (TCI). Six polymorphisms and one rare variant were identified. Among them, the –521C>T polymorphism in the promoter region of DRD4 was significantly associated with Novelty Seeking Scores and transcriptional efficiency of the gene assayed by the CAT reporter gene system. Those results suggested a contribution of dopamine D4 receptor availability to individual differences in Novelty Seeking Behavior.

Antipsychotic drug-induced obesity in rats: correlation between leptin, insulin and body weight during sulpiride treatment
A Lacruz, T Baptista, S de Mendoza, JM Mendoza-Guillén, L Hernández

Obesity associated with prolonged administration of antipsychotic drugs (AP) is an important clinical problem, that impairs health and precludes a proper pharmacological treatment. One percent of the population suffers from schizophrenia, and 50% of those people may be obese. The mechanisms of production of such a kind of obesity are difficult to explore in people, therefore, the authors have explored the effects of AP in rats. An extensive research has lately been conducted in the role of leptin in obesity. Leptin is a protein produced by the adipose tissue and other organs. It appears to inform the brain about the size of fat deposits and nutrients availability. There is a great expectation that drugs acting like leptin may help obese people to lose weight. Most obese people and rodents display high levels of leptin in blood. However, female rats rendered obese after treatment with the drug Sulpiride displayed normal levels of leptin. This means that obesity induced by AP in rats is biologically different from other types of obesity. It is also possible that obese psychiatric patients require pharmacological treatments different from those used in people with primary obesity.

Family-based linkage disequilibrium mapping using SNP marker haplotypes: application to a potential locus for schizophrenia at chromosome 22q11
T Li, D Ball, J Zhao, RM Murray, X Liu, PC Sham, DA Collier

Linkage disequilibrium (LD) mapping is a powerful method for determining the precise location of genes for complex genetic disorders such as schizophrenia. Several lines of evidence point to at least one susceptibility gene for psychosis on the long arm of chromosome 22, including the high frequency of psychosis in velocardiofacial syndrome patients with a chromosome deletion at 22q11, similar deletions in about 1% of schizophrenics, and linkage analysis. As a method of mapping potential susceptibility gene(s) in this region, the authors examined the transmission of haplotypes of

genetic markers near the catechol-O-methyltransferase gene on 22q11 from parents to offspring with schizophrenia. The authors found a five-marker haplotype which was transmitted more often than expected by chance. This may indicate that there is a haplotype in the region which can be used to identify the susceptibility allele(s) for psychosis, and the method also highlights the potential utility of extended marker haplotypes for the mapping of complex disease genes.

Comparative proteome analysis of the hippocampus implicates chromosome 6q in schizophrenia
PF Edgar, JE Douglas, GJS Cooper, B Dean, R Kydd, RLM Faull

The proteins expressed by a genome are a proteome. The authors compare hippocampal proteomes from schizophrenic and control individuals using two-dimensional gel electrophoresis, protein sequencing and computer-assisted gel comparison. In their previous study they found 18 proteins altered in concentration in the schizophrenic hippocampus, one of which was characterised as diazepam binding inhibitor. In this study, a further three proteins are characterised as: manganese superoxide dismutase, T-complex protein 1 and collapsin response mediator protein 2. Three of the four proteins characterised map to the long arm of chromosome 6, which suggests that this chromosome is important to the pathogenesis of schizophrenia. The results also indicate that antioxidant defence is altered in schizophrenia and suggest segregation distortion as a possible mechanism for the maintenance of schizophrenia susceptibility genes in the population.

Serotonin transporter gene and schizophrenia: evidence for association/linkage disequilibrium in families with affected siblings
D Hranilovic, SG Schwab, B Jernej, M Knapp, B Lerer, M Albus, M Rietschel, K Kanyas, M Borrmann, D Lichtermann, W Maier, DB Wildenauer

Alterations of the serotonin transporter affecting regulation of the serotonergic system may be involved in development of schizophrenia. A family-based design was used for studying association/linkage disequilibrium of the two polymorphisms in the serotonin transporter gene with schizophrenia. Transmission disequilibrium was observed for alleles of the intronic polymorphism (TDT = 14.33, corrected P value = 0.0003), but not for alleles of the promoter polymorphism (TDT = 0.24, P = 0.6). Our results suggest that the serotonin transporter gene itself or a gene in linkage disequilibrium with it may be implicated in the etiopathogenesis of schizophrenia.

Association between tridimensional personality questionnaire (TPQ) traits and three functional polyporphisms: dopamine receptor D4 (DRD4), serotonin transporter promoter region (5-HTTLPR) and catechol O-methyltransferase (COMT)
J Benjamin, Y Osher, M Kotler, I Gritsenko, L Nemanov, RH Belmaker, RP Ebstein

It is often assumed but rarely demonstrated that the genetics of complex human traits involves interactions between multiple genes. In the current study a complex behavioral attribute, personality traits, was ascertained using the Tridimensional Personality Questionnaire (TPQ) in 455 subjects genotyped for three common, functional and well studied polymorphisms: catechol O-methyltransferase, dopamine D4 receptor exon III (DRD4) and serotonin transporter promoter regulatory region (5-HTTLPR). Provisional evidence is presented that in this group of subjects TPQ Novelty Seeking scores are partially determined by the interactions between these three polyporphisms. The joint contribution of the three genes on NS was confirmed by both within and between family methods, taking advantage of the 159 sibling pairs recruited in this data set. Overall, our studies suggest that in both infants and adults short alleles of 5-HTTLPR and long alleles of DRD4 oppose each other's effects; ie approach behaviors (Orientation to environmental stimuli in infants and NS in adults) are promoted by long DRD4 alleles, whereas short alleles of 5-HTTLPR increase avoidance behaviors.

DRD4 exon III VNTR polymorphism—susceptibility factor for heroin dependence? Results of a case-control and a family-based association approach
P Franke, MM Nöthen, T Wang, M Knapp, D Lichtermann, H Neidt, T Sander, P Propping, W Maier

Dopaminergic abnormalities are implicated in the pathogenesis of substance abuse. The dopamine D_4 receptor gene (DRD4) is a promising candidate for mediating the genetic susceptibility to opioid dependence since two reports have been published suggesting an association between opioid dependence and prescence of long alleles of the DRD4 exon III VNTR. The authors have attempted to replicate these previous findings by employing independent case-control and family-based association samples. They found long alleles of the DRD4 exon III VNTR in similar frequency among heroin addicts and controls. Furthermore, they observed no preferential transmission of long alleles to affected offspring. These results, therefore, do not support the hypothesis that alleles of the DRD4 exon III VNTR are susceptibility factors for opioid dependence in man.

Pathological gambling and DNA polymorphic markers at MAO-A and MAO-B genes
A Ibañez, I Perez de Castro, J Fernandez-Piqueras, C Blanco, J Saiz-Ruiz

Pathological gambling is a chronic and highly disabling psychiatric disorder characterized by a persistent and recurrent maladaptive gambling behavior affecting 0.1–2.7% of the adult population. Current data suggest the involvement of biological factors in the development of this disorder and familial factors have been shown to have an important influence on risk for pathological gambling disorder. The authors studied a sample of 68 pathological gamblers and 68 unaffected individuals (47 males and 21 females in each group) in order to compare between both groups the allele distribution of

two genes which could be theoretically implicated in the pathogenesis of the disorder. They concluded that allele variants at one of the analyzed genes, that responsible for synthesis of the monoamine-oxidase A, may be a genetic liability factor in male but not female pathological gamblers of this sample, at least in most severe cases.

Modified structure of the human serotonin transporter promoter
NL Flattem, RD Blakely

The serotonin transporter (SERT, 5HTT) is a major determinant of the action of antidepressants and is also a target for psychostimulants including cocaine and amphetamines. Common variations (polymorphisms) in the promoter region of the serotonin transporter have been reported to affect the expression of this gene and have been linked to anxiety, depression and autism. The authors report a novel structure for the human serotonin transporter promoter which reveals the presence of 381 bp of DNA in between the polymorphic region and the major site for initiation of gene expression. This region contains novel regulatory sites that likely contribute to how the gene is expressed in a controlled fashion in the CNS and could impact or mediate the influence of the variable region as a risk factor for affective illness.

J Licinio, MD
Editor