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Environmental modulation of phenotype in neuregulin 1 mutants

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Abstract

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Schizophrenia, basic

ISS-01. The putative function of NR-1 in the pathophysiology of schizophrenia

ISS-01.01 DISC1, GRIK4 and NPAS3 genes contribute to the risk of developing schizophrenia, bipolar disorder and depression

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Depression is common in patients with schizophrenia and it is well established from family studies that rates of depression are increased among relatives of probands with schizophrenia. Family linkage studies in both schizophrenia and bipolar disorder have identified several chromosomal regions likely to contain risk genes for psychiatric illness and some regions overlap in schizophrenia and bipolar families suggesting common susceptibility loci. Candidate gene association studies also suggest that some genes contribute to both affective and non affective psychoses. Significant association and linkage have been reported with two of the most studied candidates, Neuregulin 1 (NR-1) and Disrupted in Schizophrenia 1 (DISC1) in schizophrenia, schizoaffective disorders, bipolar disorder and depression. However the regions associated with affective and non affective illness differ suggesting that various mutations in one gene may underlie the phenotypic differences. This is supported by an association study of DISC1 using several European cohorts of patients with bipolar disorder and schizophrenia (Hennah 2008). SNPs at two different loci showed significant association with bipolar illness and interaction of these two markers with a third SNP was also detected. These results suggest allelic and locus heterogeneity may underlie the diversity of psychiatric phenotypes. We have examined a third candidate gene for a role in both schizophrenia and affective disorders, GRIK4 a kainate ionotropic glutamate receptor mapped to chromosome 11q23 (Pickard 2006). This gene is disrupted by a chromosomal breakpoint in a patient with schizophrenia and low IQ. A case/control study show a significant association of GRIK4 with both schizophrenia and bipolar disorder and the association with schizophrenia is with markers at different domains of the gene than those showing association with bipolar disorder. The role of these three candidate genes in the pathogenesis of psychoses is not known but we can speculate that they may be involved in fundamental processes of neurodevelopment or neurogenesis increasing risk of mental disorders and the clinical phenotype as expressed in the adult will be the result of modulation by environmental factors and other genetic modifiers.

Hennah W (2008). Molecular Psychiatry (in press).
Pickard BS (2006) Molecular Psychiatry 11: 847–857.

ISS-01.02 Immunohistochemical evidence for impaired neuregulin-1 signaling in the prefrontal cortex in schizophrenia and in unipolar depression

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Objective: Neuregulin-1 proteins play roles in neuronal migration, differentiation and survival of oligodendrocytes. The NRG-1 gene codes for at least 15 different isoforms. At least four different haplotypes of the NRG-1 gene may be associated with schizophrenia. An abnormal expression pattern of NRG-1 mRNA was found in the prefrontal cortex of schizophrenic patients. Here we investigated in post-mortem brains the expression of the two NRG-1 isoforms α and β in schizophrenia.

Methods: NRG-1a was visualized by immunohistochemistry whole brain serial sections of 22 schizophrenics, 12 patients with affective disorders and 22 matched controls, NRG-1b in brains of 7 schizophrenics, 6 patients with affective disorders and 8 matched controls. NRG-1a immunoreactive material was detected with a polyclonal antiserum against human heregulin/neuregulin (antibody Ab-3 from Neomarkers), for NRG-1b we used the polyclonal antibody Ab-2 from Neomarkers. The number of profiles of NRG-1a immunoreactive neurons per hemisphere was counted using a computer assisted analysis system. NRG-1b immunopositive cells in den DLPFC and ACC were counted by using a light microscope.

Results: Normal anatomical distribution showed for NRG-1a only few immunopositive interneurons located in the prefrontal gray and white matter, whereas NRG-1β revealed a widespread immunoreactivity in pyramidal cells and interneurons in the gray matter of DLPFC and anterior cingulate cortex (ACC). In schizophrenia stereologic analysis revealed a significant reduction of NRG-1α cells in the white as well as in the gray cortical matter. In patients with unipolar depression the density of NRG-1a immunoreactive neurons was also significantly reduced in the prefrontal gray matter. In contrast to the 1α-isoform, NRG-1b immunopositive interneurons and pyramidal cells in DLPFC and ACC were significantly increased in schizophrenics in comparison to controls. Interneurons of the DLPFC differed significantly between cases of affective disorders and schizophrenics.

Conclusion: The diminished expression of NRG-1a in interstitial white matter neurons supports a neurodevelopmental component to schizophrenia (disturbed migration). With regard to NRG-1β we assume that the increase of the immunopositive neurons in schizophrenics leads to a hypofunction of NMDA-receptors via enhanced binding of this NRG-1 isoform to its receptor, ErbB4 (Hahn et al. 2006). However the increased expression of NRG-1b could also be due to the chronic administration of antipsychotics.

(1) Hahn et al. Altered neuregulin 1-erbB4 signaling contributes to NMDA receptor hypofunction in schizophrenia. Nat Med 2006 Jul; 12(7): 824–8.
(2) Bernstein HG, et al. Brain Res Bull 2006 15; 69(5): 546–59.
(3) Bertram I, et al. Ann NY Acad Sci 2007 Jan; 1096: 147–56.

ISS-01.04 Testing the functional impact of at-risk haplotypes for schizophrenia with neurobiological measures

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Neuregulin 1 has been identified as a potential susceptibility gene for schizophrenia. As with other candidate genes, initial findings have been difficult to replicate, because across studies different haplotypes were associated with the disease (Munafo et al., Schizophrenia Bulletin, 2008). SNP8NRG221533 was the single most significant variant in the original Icelandic haplotype and was included in several replication studies since then. Because neuregulin is implicated in neuronal development and synaptic transmission, we examined the impact of SNP8NRG221533 on neuropsychological, volumetric and functional measures of the brain in schizophrenia. In a study of 100 patients with first-episode of schizophrenia, SNP8_221533 was significantly associated with several measures of executive function (Trail making test B, Digit Symbol Substitution, Word fluency). A subsample of these first episode patients also underwent fMRI with an n-back paradigm. Patients without the at-risk allele at SNP8_221533 showed stronger activations in the left parahippocampal gyrus, the superior frontal gyrus, lateral temporal lobe, precuneus and the right anterior cingulate. In a separate study, we found that hippocampal brain volumes in schizophrenic patients and also in their relatives were affected by the core Icelandic haplotype comprising the same NRG1 SNP (Gruber et al., J. Psychiat Res., in press). Thus, while the association of specific SNPs and haplotpyes of the NRG1 gene with schizophrenia may appear less convincing than some years ago, NRG1 variants appear to affect brain functional and structural measures in patients and their relatives, corroborating that frequent polymorphisms (and possibly also rare mutations) in this gene impact on intermediate phenotypes of schizophrenia.

ISS-01.05 Environmental modulation of phenotype in neuregulin 1 mutants

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Objective: Schizophrenia with its multi-factorial aetiology has a concordance rate of 30–50% for monozygotic twins highlighting the fact that neither environment nor genetics alone are sufficient to cause schizophrenia but a combined action is likely. There is strong evidence that the human neuregulin 1 (NRG1) gene is a schizophrenia candidate gene and mice mutant for transmembrane domain (TM) Nrg1 exhibit a marked schizophrenia-related behavioural phenotype.

A variety of environmental risk factors have been proposed as contributing to the development of schizophrenia, including stress and chronic use of drugs of abuse. We hypothesise that subjects with a pre-existing genetic vulnerability for schizophrenia may be more susceptible to these environmental factors.

Methods: Using a multi-factorial animal model strategy, we investigated the neurobehavioural phenotype of male heterozygous TM Nrg1 mutant mice (Nrg1 HET) and their wild type-like (WT) littermates, which (i) were kept in different housing conditions [i.e. standard vs. enriched housing], or (ii) were treated acutely with drugs of abuse [i.e. amphetamine (AMP; 5 mg/kg body weight) or the psychoactive constituent of cannabis, delta-9-tetrahydrocannabinol (THC; 5/10 mg/kg body weight)]. All mice were tested in a variety of tasks for locomotion, exploration, anxiety, working memory and sensorimotor gating. Expression analyses were performed for a variety of receptor systems. Furthermore, c-Fos expression analysis determined neuronal correlates for the behavioural effects of acute THC.

Results: Nrg1 mutants were more susceptible to the stimulation of motor activity and exploration induced by environmental enrichment and its anxiolytic-like effects. Acute AMP treatment induced similar locomotor hyperactivity and disruptions of PPI as well as working memory performance in mutant and WT mice. However, Nrg1 HETs were more sensitive to the locomotor suppressant actions of THC and expressed a greater THC-induced enhancement in %PPI compared to WT mice. Mutants were also more susceptible to the anxiogenic effects of THC. Nrg1 hypomorphs expressed greater basal c-Fos levels in the shell of the nucleus accumbens and the ventrolateral septum (LSV) and a global increase in cortical serotonin 2A receptors. THC selectively increased c-Fos expression in the LSV, the central nucleus of the amygdala and the paraventricular nucleus of Nrg1 HETs.

Conclusion: These data suggest an interaction between Nrg1 and environmental factors. It appears that variation in the Nrg1 gene alters the sensitivity to the neurobehavioural effects of environmental enrichment and cannabinoids. Importantly, our study adds evidence to face and construct validity of this genetic animal model for schizophrenia.

Affective Disorders, basic

ISS-02. Dopamine and Clinical Depression: New Findings

ISS-02.01 Dopamine and the regulation of mood and motivational states in humans

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Objective: Ascending midbrain dopamine neurons project widely, innervating most motor and limbic forebrain regions. Activation of this system has been proposed to influence psychomotor activity, motivational states, and responses to rewards and punishments. Although this research has occurred primarily within the context of studies of substance abuse, Parkinson's disease, and ADHD, recent findings have rekindled interest in dopamine's potential role in mood disorders. In the following brief review, the author summarizes the history of these ideas and considers their possible relevance for understanding depression.

Methods: A systematic review of the literature using PubMed, and the keywords, depression, mood, dopamine, reward, stress, and motivation.

Results: Consistent with the animal literature, functional neuroimaging studies in humans indicate that striatal dopamine release can be elicited by a wide range of affectively relevant events, including drugs of abuse, drug-related stimuli, food and food cues, motivationally engaging video games, and psychological stressors. The behavioral significance of these changes, though, remains a subject of debate; however, studies of the effects of experimental reductions in dopamine transmission and naturally occurring brain lesions suggest that the most consistent effects are changes in (i) the initiation of movement, (ii) the ability of positively valenced stimuli to elicit and sustain focused attention, and (iii) a sense of well-being and optimistic affect. Unadulterated pleasure, in comparison, is largely unaffected.

Conclusion: The overall pattern of findings suggests that dopamine strongly influences sustained interest and approach, modestly influences positive emotions, but affects pleasure only tenuously, if at all. Together these effects could influence susceptibility to a wide range of clinically relevant symptoms, particularly psychomotor retardation, loss of interest, and a general sense of dissatisfied pessimistic apathy; the inability to experience pleasure (anhedonia), though, likely reflects disturbances to other transmitter systems.

ISS-02.02 Functional connectivity of dopamine, serotonin and norepinephrine neurons as revealed by lesion studies and antidepressant drugs

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Objective: It is well established that dopamine neurons have anatomical connections with serotonin (5-HT) and norepinephrine (NE) neurons. The importance of the functional connectivity of these reciprocal interactions had been suggested in the past from a variety of studies. However, there was scarce knowledge on the effects of sustained administration of various types of antidepressant drugs on the activity of dopamine neurons, and on the actions of dopaminergic agents effective in the treatment of depression on the activity of 5-HT and NE neurons.

Methods: In vivo electrophysiological recordings of dopamine, 5-HT, and NE neurons were carried in the brain of anesthetized rats after acute, subacute and prolonged administration of antidepressants.

Results: Sustained administration of the D2-like agonist pramipexole and of the potent NE/dopamine reuptake inhibitor nomifensine, both effective in depression, produced a transient inhibition of ventral tegmental area dopamine neurons, and a desensitization of the cell body D2-like autoreceptors. In contrast, they produced an enhancement of the firing rate of 5-HT neurons after 14 days of administration. The monoamine oxidase inhibitors phenelzine and clorgyline produced an inhibition of the firing rate of dopamine neurons which was mediated in large part by enhanced 5-HT3 receptor activation. The selective 5-HT reuptake inhibitor escitalopram produced a sustained inhibition of the firing of dopamine neurons through the activation of 5-HT2C receptors.

Conclusion: These results document the fact that various classes of antidepressants all have profound effects of the activity of the dopamine neurons giving rise to limbic and/or cortical projections. On the other hand, drugs with dopaminergic properties can also influence other monoaminergic neurons. These results provide a framework to perhaps understand treatment-resistant depression in the perspective that to obtain an optimal response, some negative feedback actions may have to be compensated for, or prevented.

ISS-02.03 Animal models of depression

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Objective: To establish an animal behavioural model of depression an attention has to be paid to behavioural changes that can be monitored objectively and are reversed by the same treatment that is effective in clinics. The most recognized animal behavioural models of depression in historical sequences are: (a) Bilateral Olfactory Bulbectomy in rodents, (b) Mother-Infant Separation in monkeys, (b) Learned Helplessness in dogs and rats (inescapable electric shocks), (c) Forced Swim Test in rodents, (d) Chronic Mild Stress in rodents, (e) Drug-withdrawal-induced anhedonia (f) Tail Suspension Test in mice, (g) Psychosocial stress in rodents (Resident-Intruder test; agonistic behaviour). The results received in potential antidepressant-like activity testing of selected drugs in rodent models of (a) olfactory bulbectomy, and (b) social stress in repeatedly defeated mice on paired agonistic interactions will be presented.

Methods: The bilateral ablation of the olfactory bulbs was performed by aspiration in the anaesthetized rats as described by Leonard and Tuite [1981]. The sham operated rats underwent the identical anaesthetic and drilling procedures as olfactory bulbectomized (OB) animals, but their bulbs were left intact. Experiments were carried out 3 weeks after the surgery. The characteristic locomotor hyperactivity in the open-field test showed by OB rats was measured in the open field (Acti-track infra-red beam based system, Panlab, s. l., Spain).

Results: (a) At the doses used none of drugs tested for their potential antidepressant-like effects (e.g. felbamate, tiagabine, sertindole, amisulpride) changed locomotor behaviour of sham-operated rats, however they inhibited locomotor hyperactivity in the open field test in OB rats. (b) Compared to control individuals the group-housed mice repeatedly defeated on interaction with aggressive singly-housed male mouse exhibit significantly higher depression of ambulation in the open field test. This was normalized by clinically proven (e.g. citalopram, valproate) as well as potential antidepressants (e.g. felbamate, rimonabant).

Conclusion: In conclusion, it is believed that drug testing in both in results presented models could predict their beneficial effect on depression.

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